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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/GB99/04426 (22) International Filing Date: 23 December 1999 (23.12.99) (30) Priority Data: 60/113,559 23 December 1998 (23.12.98) US 60/113,615 23 December 1998 (23.12.98) US 60/113,750 23 December 1998 (23.12.98) US (71) Applicant (for all designated States except MN US): ALZA CORPORATION [US/US]; 1900 Charleston Road, P.O. Box 7210, Mountain View, CA 94039-7210 (US). (71) Applicant (for MN only): ALLAN, Jamie [GB/GB]; Murgitroyd & Company, 373 Scotland Street, Glasgow G5 8QA (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): WONG, Patrick [US/US]; 1533 Burlingame Avenue, Burlingame, CA 94010 (US). EDGREN, David [US/US]; 261 Francisco Street, El Granada, CA 94018 (US). DONG, Liang-Chang [CN/US]; 181 Leota Avenue, Sunnyvale, CA 94086 (US). POLLOCK-DOVE, Crystal [US/US]; 120 Granada Drive, #15 Mountain View, CA 94043 (US).	(74) Agent: MURGITROYD & COMPANY; 373 Scotland Street, Glasgow G5 8QA (GB). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: DOSAGE FORMS COMPRISING POROUS PARTICLES		
(57) Abstract		
<p>A dosage form comprising a plurality of particles having interior pores and a liquid, active agent formulation in the pores, the particles being compactable and adapted to retain substantially all of the liquid active agent formulation within the pores during the compacting process, is described. The dosage forms may be in the forms of unitary oral forms for immediate release of active agent, prolonged delivery forms, or controlled delivery forms. All forms involve certain absorbent materials having prescribed characteristics, particularly spray dried calcium hydrogen phosphate and magnesium aluminometasilicate.</p>		

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1 DOSAGE FORMS COMPRISING POROUS PARTICLES

2

3 The present invention relates to various dosage forms
4 for the delivery of liquid active pharmaceutical agents
5 using a porous carrier which is compactable, but which
6 still retains substantially all the liquid agent in a
7 liquid form. The present invention is based on the use
8 of certain absorbent materials having prescribed
9 physical characteristics, and useable for various
10 different types of dosage forms.

11

12 From one view, it is desired to have dosage forms that
13 permit rapid release of liquid, active agent
14 formulations to facilitate absorption of the active
15 agent by the gastrointestinal tract and to minimize
16 delay in the onset of the intended beneficial effect of
17 the active agent.

18

19 Delay of onset of the beneficial effect of an active
20 agent orally administered to a subject may be
21 attributed, *inter alia*, to three basic factors:
22 firstly, the time that it takes for the active agent to

1 come into contact with the fluid environment in which
2 the active agent is to be utilized; secondly, the time
3 for the active agent to dissolve in the fluid
4 environment; and thirdly, the time for the active agent
5 to be absorbed from the gastrointestinal tract. For
6 active agents that are soluble, all three of the above
7 considerations may be addressed by the administration
8 of a solution of the liquid, active agent formulation.
9 Typically, solutions of liquid, active agent
10 formulations for pharmaceutical applications are
11 administered either from a bulk solution with the aid
12 of a device, e.g., spoon, volumetric measuring thimble,
13 or the like, that provides the desired dose of the
14 active agent to the subject, or in liquid-filled
15 gelatin capsules which provide a pre-determined dose of
16 active agent in each capsule. Dispensing from a bulk
17 solution is not always satisfactory because of the
18 difficulty of accurately measuring the dose of active
19 agent to be administered. While that usually is not
20 the case with capsules, filling of capsules is often
21 expensive and the onset of the beneficial effect of the
22 active agent may be delayed for an undesirable length
23 of time to allow for the capsule wall to dissolve and
24 release the liquid, active agent formulation to the
25 environment of use.

26

27 When the active agent is insoluble or poorly soluble,
28 the second and third considerations may be particularly
29 troublesome. Various approaches have been put forth to
30 address such problems, including the use of water-
31 soluble salts, self-emulsifying compositions,
32 polymorphic forms, powdered solutions, molecular

1 complexes, micronization, eutectics, and solid
2 solutions.

3

4 The prior art systems are primarily based on
5 incorporating drug liquid in polymeric powders, which
6 polymeric powders, such as cellulose, are insoluble in
7 aqueous media. The insoluble polymeric powders, while
8 serving to carry the drug liquid, can themselves impede
9 the rapid and complete delivery of the drug to the
10 environment of use. A critical need therefore exists
11 for dosage forms having a liquid drug carrier that is
12 soluble in the environment of use.

13

14 US Patent No. 5,846,365, which is incorporated herein
15 by reference, describes a spheronized material formed
16 from a scale-like calcium hydrogen phosphate
17 particulate material having a high specific surface
18 area, good compressibility and low friability. That
19 patent indicates that the material has the
20 characteristic of high liquid absorption. However, the
21 patent does not suggest that the material may be used
22 as a carrier for a liquid medicament formulation
23 without forming a dried, final dosage form, as for
24 example by spray drying. The patent describes the use
25 of a suspension containing medicines and binders during
26 the spray-drying granulation process to form a
27 spherical particle containing the medicine. As an
28 example, ascorbic acid in an amount equivalent to 10%
29 of the scale-like calcium hydrogen phosphate was
30 dissolved into a slurry of 20 weight percent of calcium
31 hydrogen phosphate in water, and the resulting slurry
32 was spray dried to form dried, spherical calcium

1 hydrogen phosphate containing ascorbic acid. That
2 material was then tableted under loads of 500-2000
3 kgf/cm². The calcium hydrogen phosphate is a non-
4 polymeric material which dissolves in the low pH
5 environment of the stomach.

6
7 It has been surprisingly discovered that certain
8 absorbent materials having prescribed physical
9 characteristics, as exemplified by, for example, by--
10 particular porous calcium hydrogen phosphate powders
11 described in US Patent 5,486,365, sold under the
12 trademark FujiCalin® and magnesium aluminometasilicate
13 sold under the Trade Mark Neusilin may be used to
14 prepare dosage forms in which liquid, active agent
15 formulations may be adsorbed into the interior pores of
16 the aforementioned materials in significant amounts and
17 delivered to the site of administration in the liquid
18 state. Wet granulated materials may be suitably
19 tableted by conventional methods without removal of the
20 solvent or liquid carrier of the active agent prior to
21 tableting and without deleterious exudation of the
22 liquid, active agent formulation during tableting. The
23 completed dosage forms permit the delivery of the
24 active agent to the delivery site in the liquid state,
25 thus providing minimal delay in the onset of the
26 desired beneficial effect of the active agent, since
27 the active agent does not have to be initially
28 dissolved or dispersed in the form of microparticles at
29 the site of action. Unlike powder carriers of the
30 prior art which are organic and which are insoluble in
31 aqueous media, the calcium hydrogen phosphate carrier
32 is an inorganic carrier that is soluble in gastric

1 fluids. Certain other particulates or powders, for
2 example, magnesium aluminometasilicate powders, sold
3 under the trademark Neusilin™, may also be utilized, as
4 may blends of the calcium hydrogen phosphate particles
5 and the magnesium aluminometasilicate powders.

6
7 From another view, it is desired to have a dosage form
8 being adapted to be retained in the stomach for a
9 prolonged period of time, during which a liquid, active
10 agent formulation is released to the environment of
11 use.

12
13 Controlled release dosage forms that provide for
14 prolonged delivery of active agent formulations to the
15 environment of use have found application for
16 increasing numbers of active agents. However, it has
17 generally been a problem to deliver liquid, active
18 agent formulations to the stomach of a subject
19 continuously or intermittently over a prolonged period
20 of time. Particularly when the active agent is
21 absorbed only in the upper gastrointestinal tract, the
22 bioavailability of the active agent may be greatly
23 reduced if it is rapidly released from the stomach and
24 passes quickly through the upper gastrointestinal
25 tract. The period of time for absorption may be too
26 short for an effective amount of active agent to be
27 absorbed over a reasonable period of time, without
28 frequent, subsequent dosing. This is particularly a
29 problem with liquid forms of active agents, since they
30 tend not to be retained within the stomach for more
31 than a short period of time. Instead they tend to pass
32 quickly from the stomach, through the upper

1 gastrointestinal tract and into the lower
2 gastrointestinal tract.

3

4 Generally, the time of passage of different particles
5 through the small intestine does not vary
6 significantly, and passage is generally independent of
7 food intake and particle size. Thus, active agent
8 dissolved in liquid, solid active agent dispersed in
9 liquid and relatively larger delivery units of active
10 agent, such as microcapsules and the like, will
11 traverse the length of the small intestine in
12 substantially the same time frame, usually about 3-5
13 hours. However, if liquid active agents can be
14 retained in the stomach and released over a prolonged
15 period of time, the active agent can be delivered to
16 the small intestine over a time much longer than the 3-
17 5 hour window, increasing the likelihood of increased
18 absorption.

19

20 Most active agents are not well absorbed in the
21 stomach, but even in those instances where the active
22 agent is not well absorbed, the continuous release of
23 active agent in the stomach over a prolonged time
24 period will dispense active agent over that same period
25 of time to the small intestine where it can be
26 absorbed.

27

28 The physiological behavior of the stomach is usually
29 determined by whether it contains food or is empty.
30 Food is mixed and partially digested in the distal
31 stomach (antrum). As the stomach undergoes
32 contractions, partially digested material is discharged

1 into the small intestine and non-digested material is
2 retropelled into the main part of the stomach for
3 further digestion. In the fed state, non-digestible
4 material is not generally able to leave the stomach.
5 At the end of a digestive period, the stomach enters
6 the fasting stage and begins a cycle called the
7 interdigestive myoelectric motor cycle or IMMC.

8
9 The IMMC can be considered to be divided into four
10 phases: (1) phase 1 is an approximately one hour period
11 with no contractions; (2) phase 2 is about a forty
12 minute period of intermittent potentials and
13 contractions that increase in intensity over time; (3)
14 phase 3 is a relatively short period, generally between
15 about five to fifteen minutes, of intense contractions
16 (commonly called the "housekeeper wave") that
17 completely empties the stomach; and (4) phase 4 is a
18 short transitory period between the intense activity of
19 phase 3 and the quiescence of phase 1. The different
20 phases move distally from the stomach to the terminal
21 ileum over an approximately two hour period as the
22 cycle is repeated. Since the cycle is interrupted by
23 the receipt of food by the stomach, it is possible to
24 delay the emptying phase, phase 3, by maintaining a fed
25 state. However, it is not practical to regularly
26 maintain the fed state over a long period of time.
27 Consequently, a need exists for a delivery device that
28 can remain in the stomach for a significant period,
29 whether in the fed or fasted state, and deliver active
30 agent to the stomach over a prolonged period of time.

31

1 A variety of studies have been conducted in dog and in
2 man to determine sizes of objects that would be
3 retained in the stomach during the fed stage and also
4 in the fasting stage when IMMC is present. Khosla and
5 Davis, International Journal of Pharmaceutics, Vol. 62
6 (1990), pages R9-R11 have reported that a particle size
7 less than 2 mm generally results in emptying from the
8 stomach of the dog. Non-disintegrating tablets having
9 sizes of 7, 11 and 13 mm in diameter were emptied from
10 the human stomach, but the larger sized tablets tended
11 to remain in the stomach longer than the small sized
12 tablets. Tablets larger than 11 mm tended to be
13 emptied only during the IMMC. Davis et al.,
14 Pharmaceutical Research, Vol. 8, No. 10 (1991) has
15 described retention of radio-telemetry capsules having
16 a size of 25 x 8 mm in the stomach of human subjects
17 past phase 3 of the IMMC. Timmermans et al., Journal
18 of Pharmaceutical Sciences, Vol. 82, No. 8 (1993) has
19 reported the mean resting pyloric diameter in humans as
20 12.8 ± 7.0 mm. Accordingly, it is important that
21 gastric retentive delivery vehicles are adapted to
22 disintegrate, dissolve or erode to sizes that permit
23 eventual elimination of the vehicle without causing
24 gastric obstruction.

25

26 The influence of food on gastric retention time and the
27 absorption of acyclovir has been reported in
28 International Journal of Pharmaceutics, Vol. 38 (1987),
29 pages 221-225. As reported there, compared to a
30 lighter meal, the heavier meal slowed the rate of
31 gastric emptying, prolonged small intestinal transit
32 time and decreased absorption of the active agent.

1
2 The use of albumin-cross-linked polyvinylpyrrolidone
3 hydrogels to deliver flavin mononucleotide to dogs has
4 been described by Park et al. in Journal of Controlled
5 Release, Vol.19 (1992) pages 131-134. The hydrogels
6 were maintained in the stomachs of dogs for extended
7 periods, even in the fasted state. Gels with a glassy
8 core tended to remain in the stomach longer than
9 hydrogels without the glassy core. Control of the size
10 of the core was attempted by administration of water in
11 the stomach. While it is possible to control the
12 dimensions of the hydrogel in the dry state,
13 controlling the size of the glassy core within the
14 hydrogel after administration to a subject by addition
15 of water is not suitable for fabrication of a dosage
16 form that can routinely and controllably be retained in
17 the stomach of a subject over a prolonged period of
18 time.

19
20 For many applications it may be important that the
21 delivery device is adapted to remain in the stomach for
22 a prolonged period. For certain applications it may
23 also be important that the device deliver active agent
24 in a controlled manner. Delivery systems, such as
25 those described below, are representative of the many
26 different systems have been suggested for such
27 controlled delivery of active agents over a prolonged
28 period of time.

29
30 U.S. Patent No. 5,534,263, which is incorporated herein
31 by reference, describes a dosage form useful for the
32 prolonged delivery of an active agent formulation in

1 the form of a matrix having two or more insoluble bands
2 on the surface of the matrix. The exposed surfaces of
3 the matrix erode in a manner that creates additional
4 surface areas to provide for prolonged release of an
5 active agent formulation with determined release
6 profiles.

7
8 Generally the previous systems have been directed to
9 the delivery of active agents which are in the dosage
10 forms initially in the dry state. Little effort
11 appears to have been made to deliver liquid active
12 agent formulations that would be retained in the
13 stomach for a sustained period of time. Administration
14 of acyclovir by sipped solution over a four-hour period
15 has been described in Br. J. clin. Pharmac., 21, 459-
16 462 (1986) to achieve an increased contact time with
17 the human stomach and the gastrointestinal tract. The
18 total amount of acyclovir absorbed was increased over
19 that observed with administration of acyclovir tablets.
20 However, no attempt was made to maintain the acyclovir
21 solution in the stomach for a sustained period except
22 by continuous oral administration.

23
24 Furthermore, when the active agent is insoluble or
25 poorly soluble, prior art systems may not provide
26 suitable delivery of active agent or concentration
27 gradients at the site of absorption for that period of
28 time that the active agent sees the absorption site.
29 Various attempts have been made to address such
30 problems, including the use of water-soluble salts,
31 self-emulsifying compositions, polymorphic forms,
32 powdered solutions, molecular complexes, micronization,

1 eutectics, and solid solutions, in the context of
2 immediate release delivery. An example of the use of a
3 powdered solution is described by Sheth, et al., in
4 "Use of Powdered Solutions to Improve the Dissolution
5 Rate of Polythiazide Tablets," Drug Development and
6 Industrial Pharmacy, 16(5), 769-777 (1990). References
7 to certain of the other approaches are cited therein.
8 Additional examples of powdered solutions are described
9 in US Patent 5,800,834. The patent describes
10 methodology for calculating the amount of liquid that
11 may be optimally sorbed into materials to prevent the
12 drug solution from being exuded from the granular
13 composition during compression.

14
15 As can be observed in the above-referenced patents and
16 publications, devices have been described that provide
17 for prolonged delivery of an active agent and retention
18 in the gastric environment. However, there remains a
19 continuing need for improved systems for delivering a
20 liquid, active agent formulation to the gastric
21 environment over a prolonged period of time and in a
22 reliable, controllable and reproducible manner. In
23 particular, there is a need for controlled release
24 delivery devices that are to remain in the stomach,
25 even during a fasting state in which IMMC is present,
26 for a prolonged period, for example from about 3 hours
27 to up to about 20-24 hours, and deliver a liquid,
28 active agent formulation. Such devices should exhibit
29 a combination of flexibility and rigidity so as not to
30 be expelled from the stomach into the pyloric sphincter
31 under fed or fasting conditions, and deliver active

1 agent in a reproducible, controlled manner, over a
2 prolonged period of time.

3

4 From another view, it is desired to have improved
5 methods, dosage forms and devices for the controlled
6 delivery of liquid active agent formulations to an
7 environment of use.

8

9 Administration of liquid, active agent formulations is
10 often preferred over solid active agent formulations in
11 order to facilitate absorption of the active agent and
12 obtain a beneficial effect for the intended use in the
13 shortest possible time after the formulation is exposed
14 to the environment of use. Examples of prior art
15 devices to deliver liquid, active agent formulations
16 are soft gelatin capsules that contain a liquid active
17 agent formulation or liquid formulations of the active
18 agent that are bottled and dispensed in measured dosage
19 amounts by the spoonful, or the like. Those systems
20 are not generally amenable to controlled delivery of
21 the active agent over time. While it is desired to
22 have the active agent exhibit its effect as soon as it
23 is released to the environment of use, it also often is
24 desirable to have controlled release of the active
25 agent to the environment of use over time. Such
26 controlled release may be sustained delivery over time,
27 such as zero order, or patterned delivery, such as
28 pulsatile for example. Prior art systems have not
29 generally been suitable for such delivery.

30

31 Various devices and methods have been described for the
32 continuous delivery of active agents over time.

1 Typically, such prior art systems have been used to
2 deliver active agents initially in the dry state prior
3 to administration. For example, US Patent
4 Nos. 4,892,778 and 4,940,465, which are incorporated
5 herein by reference, describe dispensers for delivering
6 a beneficial agent to an environment of use that
7 include a semipermeable wall defining a compartment
8 containing a layer of expandable material that pushes a
9 drug layer out of the compartment formed by the wall.
10 The exit orifice in the device is substantially the
11 same diameter as the inner diameter of the compartment
12 formed by the wall.

13
14 US Patent No. 4,915,949, which is incorporated herein
15 by reference, describes a dispenser for delivering a
16 beneficial agent to an environment of use that includes
17 a semipermeable wall containing a layer of expandable
18 material that pushes a drug layer out of the
19 compartment formed by the wall. The drug layer
20 contains discrete tiny pills dispersed in a carrier.
21 The exit orifice in the device is substantially the
22 same diameter as the inner diameter of the compartment
23 formed by the wall.

24
25 US Patent No. 5,126,142, which is incorporated herein
26 by reference, describes a device for delivering an
27 ionophore to livestock that includes a semipermeable
28 housing in which a composition containing the ionophore
29 and a carrier and an expandable hydrophilic layer is
30 located, along with an additional element that imparts
31 sufficient density to the device to retain it in the
32 rumen-reticular sac of a ruminant animal. The ionophore

1 and carrier are present in a dry state during storage
2 and the composition changes to a dispensable, fluid-
3 like state when it is in contact with the fluid
4 environment of use. A number of different exit
5 arrangements are described, including a plurality of
6 holes in the end of the device and a single exit of
7 varying diameter to control the amount of drug released
8 per unit time due to diffusion and osmotic pumping.

9
10 It is often preferable that a large orifice, from about
11 50%-100% of the inner diameter of the drug compartment,
12 be provided in the dispensing device containing the
13 active agent and a bioerodible or degradable active
14 agent carrier. When exposed to the environment of use,
15 drug is released from the drug layer by erosion and
16 diffusion. In those cases where the drug is present in
17 the solid state, the realization of the beneficial
18 effect is delayed until the drug is dissolved in the
19 fluids of the environment of use and absorbed by the
20 tissues or mucosal environment of the gastrointestinal
21 tract. Such delay often is not tolerable. Also, for
22 drugs that are poorly soluble in gastric or intestinal
23 fluids, the delay may be further exacerbated.

24
25 Devices in which the drug composition initially is dry
26 but in the environment of use is delivered as a slurry,
27 suspension or solution from a small exit orifice by the
28 action of an expandable layer are described in U. S.
29 Patents Nos. 5,660,861, 5,633,011; 5,190,765;
30 5,252,338; 5,620,705; 4,931,285; 5,006,346; 5,024,842;
31 and 5,160,743. Typical devices include an expandable
32 push layer and a drug layer surrounded by a

1 semipermeable membrane. In certain instances, the drug
2 layer is provided with a subcoat to protect the drug
3 composition in those portions of the gastrointestinal
4 tract having acidic pH, to delay release of the drug
5 composition to the environment of use or to form an
6 annealed coating in conjunction with the semipermeable
7 membrane. However, such devices often are not well
8 suited for the delivery of active agents that
9 demonstrate instability over time in the fluids with
10 which they come in contact in the environment of use.
11 Attempts have been made to protect the active agent
12 from the environment of use by stabilizing agents,
13 enteric coatings and the like. However, stabilization
14 methods and coatings may delay the absorption of the
15 active agent with concomitant delay in realized
16 beneficial effect. Also, such systems may not generally
17 be amenable to controlled delivery of active agent in
18 the liquid state.

19
20 Furthermore, when the active agent is insoluble or
21 poorly soluble, prior art systems may not provide rapid
22 delivery of active agent or concentration gradients at
23 the site of absorption that facilitate absorption
24 through the gastrointestinal tract. Various approaches
25 have been put forth to address such problems, including
26 the use of water-soluble salts, self-emulsifying
27 compositions, polymorphic forms, powdered solutions,
28 molecular complexes, micronization, eutectics, and
29 solid solutions. An example of the use of a powdered
30 solution is described by Sheth, et al., in "Use of
31 Powdered Solutions to Improve the Dissolution Rate of
32 Polythiazide Tablets," Drug Development and Industrial

1 Pharmacy, 16(5), 769-777 (1990). References to certain
2 of the other approaches are cited therein. Additional
3 examples of powdered solutions are described in US
4 Patent 5,800,834. The patent describes methodology for
5 calculating the amount of liquid that may be optimally
6 sorbed into materials to prevent the drug solution from
7 being exuded from the granular composition during
8 compression.

9
10 It has been surprisingly discovered that certain
11 absorbent materials having prescribed physical
12 characteristics, as exemplified by, for example,
13 particular porous calcium hydrogen phosphate powders
14 described in US Patent 5,486,365, already discussed
15 herein, and sold under the trademark FujiCalin®, may be
16 used to prepare dosage forms in which liquid, active
17 agent formulations may be adsorbed into the interior
18 pores of the aforementioned materials in significant
19 amounts and delivered to the site of administration in
20 the liquid state. It has further been surprisingly
21 discovered that such types of porous particles with
22 liquid, active agent formulations sorbed into the
23 particles may be fabricated into controlled release
24 dosage forms without exuding the liquid, active agent
25 formulation out of the particles during the
26 manufacturing process. That discovery has permitted
27 the fabrication of controlled release dosage forms that
28 provided for the delivery of the active agent to the
29 delivery site in the liquid state, thus providing
30 minimal delay in the onset of the desired beneficial
31 effect of the active agent, since the active agent does
32 not have to be initially dissolved or dispersed in the

1 form of microparticles at the site of action.
2 Furthermore, such dosage forms permit the delivery of
3 high concentrations of active agent, and optionally
4 absorption enhancers, to the absorption site. Other
5 particles having the characteristics of the calcium
6 hydrogen phosphate as described herein and sold under
7 the trademarks of FujiCalin, such as, for example,
8 magnesium aluminometasilicate powders, sold under the
9 trademark Neusilin™, may also be utilized.

10
11 According to one aspect of the present invention, there
12 is provided a dosage form comprising a plurality of
13 particles having interior pores and a liquid, active
14 agent formulation in the pores, the particles being
15 compactable and adapted to retain substantially all of
16 the liquid active agent formulation within the pores
17 during the compacting process.

18
19 Preferably, the particles are formed from calcium
20 hydrogen phosphate, microcrystalline cellulose, silicon
21 dioxide, or magnesium aluminosilicate, or blends
22 thereof.

23
24 In one embodiment of the present invention, the
25 particles formed from calcium hydrogen phosphate may
26 have the following general formula



28 wherein m satisfies the relationship $0 \leq m \leq 2.0$.

29
30 In one form, the particles are formed by spray drying a
31 scale-like calcium hydrogen phosphate with a specific
32 surface area of 20 m²/g to 60 m²/g, an apparent specific

1 volume of 1.5 ml/g or more, an oil absorption capacity
2 of 0.7 ml/g or more, a primary particle size of 0.1μ to
3 5μ , and an average particle size of 2μ to 10μ among
4 secondary particles that are aggregates of the primary
5 particles.

6
7 In another form, the particles are calcium hydrogen
8 phosphate having a specific volume of at least
9 1.5 ml/g, a BET specific area of at least $20\text{ m}^2/\text{g}$, and a
10 water absorption capacity of at least 0.7 ml/g.

11
12 In another form, the particles have a bulk density of
13 $0.4\text{-}0.6\text{ g/ml}$, a BET surface area of $30\text{-}50\text{ m}^2/\text{g}$, a
14 specific volume of greater than 1.5 ml/g, and a mean
15 pore size of at least 50 Angstroms.

16
17 In another form, the particles are calcium hydrogen
18 phosphate having a bulk specific volume of 1.5 ml/g-
19 5 ml/g, a BET specific area of $20\text{ m}^2/\text{g}$ - $60\text{ m}^2/\text{g}$, a water
20 absorption capacity of at least 0.7 ml/g, and a mean
21 particle size of at least 70 microns.

22
23 Preferably, the porous particles have a size
24 distribution of 100% less than 40 mesh, 50%-100% less
25 than 100 mesh and 10%-60% less than 200 mesh, more
26 preferably 60%-90% are less than 100 mesh and 20%-60%
27 are less than 200 mesh.

28
29 In another embodiment of the present invention, the
30 particles are magnesium aluminometasilicate represented
31 by the general formula

32 $\text{Al}_2\text{O}_3\text{MgO}\cdot 2\text{SiO}_2\cdot n\text{H}_2\text{O}$

1
2 wherein n satisfies the relationship $0 \leq n \leq 10$. The
3 particles may comprise magnesium aluminometasilicate
4 powder.

5
6 The dosage form may include a pH regulating agent
7 selected from one or more of the group comprising
8 organic acids, inorganic acids and bases, and/or
9 include a chelating agent. In particular, it has been
10 found that the use of organic acid(s) and/or chelating
11 agent(s) facilitate the dissolution of FujiCalin
12 particles upon contact with gastric acid.

13
14 Preferably, the weight percent of a liquid, active
15 agent formulation is at least 5% of the total weight of
16 the dosage form.

17
18 These absorbent materials have been found to be useful
19 for various types of dosage forms.

20
21 In one embodiment of the present invention, the dosage
22 form is adapted for rapid, possibly immediate, release
23 of the active agent. The active agent for this could
24 be selected from active agents that have low water
25 solubility, such as for example sildenafil citrate,
26 acetaminophen, ibuprofen or ketoprofen.

27
28 In the capsule form, the particles are preferably to
29 bind themselves in a dosage form such a gelatin capsule
30 or a tablet. The particles could be dispersed in a
31 liquid to form a paste adapted for loading into a
32 gelatin capsule, and be calcium hydrogen phosphate

1 having a specific volume of at least 1.5 ml/g, a BET
2 specific area of at least 20 m²/g, and a water
3 absorption capacity of at least 0.7 ml/g. The liquid
4 forming the paste with the particles could be the same
5 liquid as the liquid of the liquid, active agent
6 formulation.

7
8 The completed dosage forms permit the delivery of the
9 active agent to the site of action in the liquid state,
10 thus providing minimal delay in the onset of the
11 desired beneficial effect of the active agent since the
12 active agent does not have to be initially dissolved or
13 dispersed in the form of microparticles at the site of
14 action. Certain magnesium aluminometasilicate powders,
15 sold under the trademark Neusilin™, or blends of
16 FujiCalin and Neusilin, may also be utilized to afford
17 dosage forms of the present invention.

18
19 In a second embodiment of the present invention, the
20 dosage form is such that the porous particles can be
21 dispersed in a bioerodible carrier. The bioerodible
22 carrier preferably swells upon imbibing fluid from
23 stomach so as to be retained within the stomach of a
24 subject for a prolonged period of time.

25
26 The bioerodible carrier preferably comprises a polymer
27 matrix formed of a mixture of a swellable, water
28 soluble polymer that expands when in contact with
29 fluids in the gastric environment and a
30 hydroattractant.

31

1 The matrix could be formed with a rigid or semi-rigid
2 segment in which swelling of the matrix is constrained
3 to provide a rigid or semi-rigid section in the dosage
4 form that facilitates the dosage form remaining in the
5 stomach of a subject over a prolonged period of time.
6 The rigid or semi-rigid section of the dosage form
7 preferably comprises one or more insoluble materials,
8 having low water permeability and formed as a band
9 circumscribing a portion of the surface of the matrix,
10 that along with the banded portion of the polymer
11 matrix forms the rigid or semi-rigid segment of the
12 dosage form.

13
14 In one form, the dosage form comprises (a) a
15 therapeutically-effective amount of a liquid, active
16 agent formulation sorbed into porous particles, (b) a
17 polymer matrix in which the porous particles are
18 dispersed, the polymer matrix including a high
19 molecular weight, water-soluble polymer and a
20 hydroattractant, the polymer matrix having an outer
21 surface for exposure to the environment of use, and (c)
22 a band of insoluble material circumscribing a portion
23 of the outer surface of the polymer matrix.

24
25 The hydroattractant is preferably a water-insoluble
26 polymer, and the polymer matrix could further include
27 non-polymeric water-soluble excipients and polymers of
28 molecular weight of less than 10,000 grams per mole.
29 The weight percent of the water soluble, high molecular
30 weight polymer could be about 10 to 50 weight percent
31 and the weight percent of the hydroattractant could be
32 about 5 to 70 weight percent.

1
2 In another form, the dosage form of this embodiment,
3 comprises a unitary compressed dispersion of a liquid,
4 active agent formulation in a plurality of porous
5 particles in a gel-forming, erodible polymer matrix
6 having a first portion that swells in the stomach while
7 maintaining its physical integrity for a prolonged
8 period of time and a second, non-erodible, non-gel-
9 forming portion for promoting retention of the dosage
10 form in the stomach over a prolonged period of time.

11
12 In general, the number average molecular weight of the
13 water-soluble polymer can be between about 100,000 and
14 20,000,000 grams per mole, such as for example one or
15 more of the group comprising polyethylene oxide,
16 hydroxypropyl cellulose, hydroxypropyl methyl
17 cellulose, hydroxyethyl cellulose, sodium carboxyl
18 methylcellulose, calcium carboxymethyl cellulose,
19 methyl cellulose, polyacrylic acid, maltodextrin, pre-
20 gelatinised starch or polyvinyl alcohol.

21
22 The hydroattractant is preferably one or more of the
23 group comprising low-substituted hydroxypropyl
24 cellulose, microcrystalline cellulose, cross-linked
25 sodium or calcium carboxymethyl cellulose, cellulose
26 fiber, cross-linked polyvinyl pyrrolidone, cross-linked
27 polyacrylic acid, cross-linked Amberlite resin,
28 alginates, colloidal magnesium-aluminum silicate, corn
29 starch granules, rice starch granules, potato starch
30 granules or sodium carboxymethyl starch.

31

1 This form of dosage form is adapted for gastric
2 retention, and could be used wherein the active agent
3 is one or more of the group comprising an antiviral,
4 antimicrobial, antidiabetic, antihyperglycemic,
5 hypoglycemic, antidepressant, antiobesity,
6 immunosuppressive, antidiabetic or antifungal active
7 agent, such as for example acyclovir, ganciclovir,
8 cimetidine, ranitidine, captopril, methyldopa,
9 selegiline, minocycline, metformin, bupropion,
10 orlistat, cyclosporin, cyclosporine, metaspurin or
11 fexofenadine or a pharmaceutically acceptable salt
12 thereof.

13
14 This dosage form could also release the active agent
15 from the porous particles in a liquid formulation to
16 the gastrointestinal tract over a time period of at
17 least 3 hours, and/or act as a gastric-emptying delaying
18 agent. Suitable gastric-emptying delaying agents
19 include anticholinergic agents, methylcellulose, guar
20 gum, fats such as triglyceride esters, and fatty acids
21 of 10-15 carbon atoms.

22
23 This embodiment of the present invention provides a
24 dosage form that is retained in the stomach for a
25 prolonged period of time and that is useful for the
26 prolonged delivery of a liquid, active agent
27 formulation to a fluid environment of use. Certain
28 embodiments of the invention provide for initial and
29 substantially complete delivery of a liquid, active
30 agent formulation in the stomach of a user, where the
31 active agent may be absorbed or released from the
32 stomach to be absorbed in the gastrointestinal tract.

1 In particular applications the gastric retentive dosage
2 forms of the invention may allow for less frequent,
3 dosing of the active agent than with immediate release
4 formulations or sustained release formulations that are
5 not gastric retentive dosage forms. In other
6 applications the frequency of dosing may be the same,
7 but the gastric retentive dosage forms will
8 beneficially alter the absorption profile of the active
9 agent from that available with immediate release
10 formulations. This may result in increased
11 bioavailability of the active agent or reduced side
12 effects, for example.

13

14 Microcrystalline cellulose and silicon dioxide having
15 high surface area and good absorption properties may
16 especially be used in these dosage forms.

17

18 For this embodiment of the present invention, the
19 following definitions are used.

20

21 The phrase "prolonged period" or "prolonged period of
22 time" intends a time period that lasts for several
23 hours to about 24 hours, usually up to about 12 hours,
24 and often between about 3 and 14 hours, and most often
25 at least 6 hours.

26

27 The phrase "prolonged delivery" intends a duration of
28 delivery extending over a time period that lasts for
29 several hours to about 24 hours, usually up to about 12
30 hours, and often between about 3 and 14 hours, and most
31 often at least 6 hours.

32

1 By "insoluble" is intended a material that will not
2 substantially dissolve in the environment of use during
3 the delivery period.

4
5 The term "active agent" refers to an agent, drug,
6 compound or other substance, or compositions and
7 mixtures thereof, that provide some pharmacologic,
8 often beneficial, effect. Reference to a specific
9 active agent shall include where appropriate the active
10 agent and its pharmaceutically acceptable salts and may
11 include mixtures of active agents.

12
13 The term "polymer matrix" as used herein means a
14 mixture of a water soluble, high molecular weight
15 polymer and a hydroattractant.

16
17 The term "liquid, active agent formulation" intends a
18 solution, suspension or dispersion of the active agent
19 or the active agent optionally in combination with
20 pharmaceutically acceptable carriers and additional
21 inert ingredients, in a liquid.

22
23 The terms "adapted for gastric retention" or "gastric
24 retentive" mean, with respect to the dosage form of
25 this invention, that the dosage form will remain in the
26 stomach of a subject for a prolonged period of time.

27
28 The terms "rigid" and "semi-rigid" mean, with respect
29 to a portion of the active agent formulation matrix or
30 polymer matrix as defined above, that such portion will
31 not swell and form a gel when initially contacted with
32 gastric fluid.

1
2 The term "bioerodible" intends a material that will, at
3 least in part, dissolve, degrade or erode in the fluid
4 environment of use.

5
6 The term "bioequivalent" intends, with respect to an
7 active agent dosage form of this invention, that there
8 is greater than a 90% probability that the
9 bioavailability of the active agent as determined by
10 standard methods is 80-125% of the defined dosage form
11 and that there is greater than a 90% probability that
12 the maximum blood plasma concentration and the minimum
13 blood plasma concentration of the active agent as
14 measured by standard methods is 80-125% of the defined
15 dosage form.

16
17 The term "polymer" means a material formed from a
18 single polymer or a mixture of polymers.

19
20 The term "swellable" means, with respect to a polymer
21 or a polymer matrix, that the polymer or polymer matrix
22 is capable of imbibing fluid and expanding when in
23 contact with fluid present in the environment of use.

24
25 The terms "therapeutically effective" amount or rate
26 refer to the amount or rate of the active agent needed
27 to effect the desired pharmacologic, often beneficial,
28 result.

29
30 The dosage forms of this form of the invention find
31 use, for example, in humans or other animals. The
32 environment of use is a fluid environment and for the

1 purposes of this invention primarily includes the fluid
2 environment of the stomach and the upper intestinal
3 tract or small intestine. A single dosage form or
4 several dosage forms can be administered to a subject
5 during a therapeutic program.

6
7 In a third embodiment of the present invention, there
8 is a dosage form for sustained or pulsatile release of
9 active agent. In general there is a dosage form for an
10 active agent comprising a wall defining a cavity, the
11 wall having an exit orifice formed or formable therein
12 and at least a portion of the wall being semipermeable;
13 an expandable layer located within the cavity remote
14 from the exit orifice and in fluid communication with
15 the semipermeable portion of the wall; a drug layer
16 located within the cavity adjacent the exit orifice and
17 in direct or indirect contacting relationship with the
18 expandable layer, wherein the drug layer is a form
19 defined by the dosage forms defined herein above

20
21 In certain embodiments, there is a placebo layer
22 between the exit orifice and the drug layer, and/or a
23 flow-promoting layer interposed between the inner
24 surface of the wall and at least the external surface
25 of the drug layer located within the cavity. There may
26 be two drug layers separated by at least one inert
27 layer, possibly with each of said drug layers
28 containing a different active agent.

29
30 For this form of dosage form, the liquid, active agent
31 formulation of the drug layer preferably comprises a
32 self-emulsifying formulation, and has low water

1 solubility. The liquid active agent of the drug layer
2 may also comprise an absorption enhancer, and the
3 liquid, active agent formulation preferably comprises
4 at least 30% by weight of the drug layer.

5
6 This form of dosage form may be adapted for sustained
7 or pulsatile release of the liquid, active agent
8 formulation upon administration to a subject.

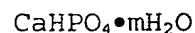
9 In general, the dosage forms of the present invention
10 are in a unitary and oral dosage form.

11

12 The present invention also covers a composition
13 comprising from about 1 to 50 weight percent of porous
14 calcium hydrogen phosphate particles having sorbed
15 therein a liquid, active agent formulation, about 5
16 weight percent to about 50 weight percent of a
17 polyethylene oxide polymer having a number average
18 molecular weight of between about 100,000 and
19 20,000,000 grams per mole and about 5 weight percent to
20 about 60 weight percent of a hydroxypropyl cellulose
21 polymer having a hydroxypropyl content of between about
22 10 weight percent and about 13 weight percent of the
23 hydroxypropyl cellulose polymer the porous particles
24 comprising calcium hydrogen phosphate with a specific
25 surface area of 20 m²/g to 60 m²/g, an apparent specific
26 volume of 1.5 ml/g or more, an oil absorption capacity
27 of 0.7 ml/g or more, and a mean particle size of
28 greater than 70 microns, the calcium hydrogen phosphate
29 being represented by the following general formula:

30

31



32

1 wherein m satisfies the relationship $0 \leq m \leq 2.0$, or
2 a composition comprising a liquid formulation of the
3 active-agent sorbed into a plurality of porous
4 particles, the particles being formed by spray drying a
5 scale-like calcium hydrogen phosphate with a specific
6 surface area of $20 \text{ m}^2/\text{g}$ to $60 \text{ m}^2/\text{g}$, an apparent specific
7 volume of 1.5 ml/g or more, an oil absorption capacity
8 of 0.7 ml/g or more, a primary particle size of 0.1μ to
9 5μ , and an average particle size of 2μ to 10μ among
10 secondary particles that are aggregates of the primary
11 particles, the scale-like calcium hydrogen phosphate
12 being represented by the following general formula:



14 wherein m satisfies the relationship $0 \leq m \leq 2.0$, and
15 dispersed throughout a bioerodible carrier, the
16 particles being released in the environment of use over
17 a prolonged period of time.

18

19 In further aspects of the present invention, there are
20 provided the following methods;

21

22 A method of manufacturing a dosage form comprising
23 contacting a plurality of particles having interior
24 pores as defined hereinbefore with a liquid, active
25 agent formulation, and compacting the particles into a
26 dosage form without removing all of the liquid from the
27 liquid, active agent formulation.

28

29 Preferably, the particles are spherical calcium
30 hydrogen phosphate particles obtained by spray drying a
31 scale-like calcium hydrogen phosphate or magnesium
32 aluminometasilicate particles as hereinbefore defined.

1 Also preferably, less than 80% of the liquid of the
2 active agent formulation is removed prior to the
3 compacting step.

4
5 A method of facilitating the release of an active agent
6 from a dosage form comprising sorbing a liquid
7 formulation of the active agent into a plurality of
8 porous particles, the particles being formed as defined
9 hereinbefore, and dispersing the particles throughout a
10 bioerodible carrier.

11
12 A method for facilitating the immediate release of an
13 active agent from a dosage form containing a liquid,
14 active agent formulation sorbed into a porous particle,
15 wherein the dissolution rate of the porous particle is
16 pH sensitive, comprising incorporating a pH regulating
17 agent into the dosage form to bias the pH of the
18 microenvironment of the porous particle after
19 administration toward a pH increasing the rate of
20 dissolution of the porous particle.

21
22 Preferably, the pH regulating agent is an organic acid,
23 and inorganic acid or a base, more preferably the
24 particle is a calcium hydrogen phosphate and the pH
25 regulating agent is an organic acid.

26
27 Embodiments of the present invention will now be
28 described by way of example only and with reference to
29 the accompanying drawings in which:

30
31 Figure 1 is a dosage form according to one embodiment
32 of the present invention.

1
2 Figures 2A, 2B and 2C illustrate a second embodiment of
3 the delivery device of the present invention; the
4 device in Figure 2A representing the active agent
5 formulation matrix not including the insoluble material
6 or band, the device in Figure 2B representing the
7 banded device in prepared form prior to placement in
8 the stomach; and Figure 2C illustrating a porous
9 particle having liquid, active agent sorbed therein.

10
11 Figure 3 illustrates the device of Figure 2B in its
12 initially-swollen state after having expanded in the
13 stomach;

14
15 Figures 4A and 4B illustrate the device of Figure 3 at
16 later stages where the device has eroded in the fluid
17 environment of use;

18
19 Figures 5A-5D illustrate an embodiment of the invention
20 having multiple, insoluble bands on the surface of the
21 dosage form.

22
23 Figure 6 illustrates a dosage form of one design of
24 third embodiment of the present invention adapted for
25 zero order release of active agent;

26
27 Figure 7 illustrates a dosage form of another design of
28 the third embodiment of this invention adapted to
29 deliver a delayed pulse of the active agent;

30
31 Figure 8 illustrates the release profile (release rate
32 as a function of time) of the active agent progesterone

1 from a representative dosage form of the invention
2 having zero order release;

3

4 Figures 9-13 illustrate the release profiles (percent
5 of active agent released as a function of time) of the
6 active agent progesterone for representative dosage
7 forms of the invention having a delayed pulse release,
8 wherein the initial delay is 2 hours, 3 hours, 4-5
9 hours, 6-7 hours and about 10 hours for the dosage
10 forms described in Examples 12-16 respectively; and

11

12 Figures 14-17 illustrate various dissolution and
13 release profiles relating to dosage forms described in
14 Examples 17 and 18.

15

16

17 An embodiment of a rapid, possibly immediate release
18 dosage form of the invention is illustrated in FIG. 1.
19 In FIG. 1, dosage form 1 comprises a plurality of
20 particles 2 having a plurality of interior and surface
21 pores 4. Absorbed into the interior of pores 4 is a
22 liquid, active agent formulation 6. Particles 2 are
23 compacted to form a tableted, unitary dosage form 1
24 from which the active agent formulation 6 may be
25 delivered to the site of action in the liquid form,
26 thus avoiding delayed onset of activity of the active
27 agent.

28

29 Materials useful as carriers for the liquid, active
30 agent formulations for all forms of the present
31 invention are porous particulates that are
32 characterized by high compressibility or tensile

1 strength to withstand compacting forces applied during
2 compacting steps and minimize exudation of liquid,
3 active agent formulation from the pores; particle flow
4 characteristics that allow for the porous particles to
5 be directly compacted without the use of a binder or
6 with minimal use of a binder; low friability so as to
7 preclude or minimize exudation of the liquid, active
8 agent formulation from the particles during compacting
9 steps; and high porosity so as to absorb an adequate of
10 amount of a liquid, active agent formulation to provide
11 an effective amount of active agent in a dosage form.
12 The particles should be adapted to absorb an amount of
13 liquid, active agent formulation such that a
14 therapeutically effective amount of the active agent
15 may be delivered in a unitary dosage form that is of a
16 size that can be conveniently swallowed by a subject
17 and, preferably provided in four or fewer tablets or
18 capsules for ingestion at the same time. The porosity
19 of the particles should be such that at least 5% of the
20 liquid, active agent is sorbed into the pores of the
21 particles. Typically, up to 70% by weight, and usually
22 in the range 20-70%, more preferably 30-60%, and most
23 preferably 40-60% of the liquid, active agent
24 formulation, based on the weight of the particles, may
25 be sorbed into the pores of the particles, while the
26 particles exhibit sufficient strength at such degree of
27 liquid, active agent loading so as not to significantly
28 be crushed or pulverized by compacting forces to which
29 the particles will be subjected during manufacturing
30 operations. Preferably, the loading of the liquid,
31 active agent formulation will be on the order of at
32 least 30-40 weight percent when the particles are

1 crystalline, such as calcium hydrogen phosphate. When
2 the particles are amorphous, such as with magnesium
3 aluminometasilicate, greater loading burdens may
4 usually be achieved, e.g. up to 60% by weight. At high
5 loadings, it may be advantageous to use blends of
6 calcium hydrogen phosphate particles and the amorphous
7 magnesium aluminometasilicate powders.

8

9 Preferred materials are those having a strength to
10 resist compression forces of greater than 1500 kg/cm²
11 without substantial exudation of the liquid, active
12 agent formulation, and most preferably without the
13 tablet hardness plateauing.

14

15 A particularly suitable carrier is exemplified by the
16 particular form of calcium hydrogen phosphate described
17 in U.S. Patent No. 5,486,365, which is incorporated
18 herein by reference. As described therein, calcium
19 hydrogen phosphate is prepared by a process yielding a
20 scale-like calcium hydrogen phosphate that can be
21 represented by the formula $\text{CaHPO}_4 \cdot m\text{H}_2\text{O}$ wherein m
22 satisfies the expression $0 \leq m \leq 2.0$. The scale-like
23 calcium hydrogen phosphate produced has characteristic
24 physical properties that make it particularly suitable
25 for use in the present invention. The scale-like
26 material provides high specific surface area, high
27 specific volume, high capacity for water and oil
28 absorption, and the ability to readily form into
29 spheres upon spray drying. The spherical particulates
30 have excellent flow properties and permit direct
31 compaction into tablets with minimal or no use of

1 binders and without significant crushing or pulverizing
2 of the particles during the compaction step.

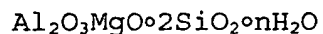
3
4 The scale-like calcium hydrogen phosphate particles
5 generally have a BET specific surface area of at least
6 $20 \text{ m}^2/\text{g}$, typically $20 \text{ m}^2/\text{g}$ - $60 \text{ m}^2/\text{g}$, a specific volume
7 of at least 1.5 ml/g , typically $2\text{-}5 \text{ ml/g}$ or more, and
8 an oil and water absorption capacity of at least 0.7
9 ml/g , typically $0.8\text{-}1.5 \text{ ml/g}$. When formed into spheres
10 the spherical particulates may have a mean particle
11 size of at least 70 microns, usually about 70-130
12 microns, and often about 90-120 microns. The particle
13 size distribution may be 100% through 40 mesh, 50%-100%
14 through 100 mesh, and 20%-60% through 200 mesh. The
15 bulk density may be from about 0.4 g/ml - 0.6 g/ml .

16
17 A most preferred form of calcium hydrogen phosphate is
18 that sold under the trademark FujiCalin by Fuji
19 Chemical Industries (U.S.A.) Inc., Englewood, New
20 Jersey, in types SG and S. Typical parameters for that
21 material include a mean pore size on the order of 70
22 Angstroms, a mean particle size of about 110 microns, a
23 specific volume of about 2 ml/g , a BET specific surface
24 area of about $30\text{-}40 \text{ m}^2/\text{g}$, and an oil and water
25 absorption capacity of about 0.8 ml/g . Type SG
26 typically will have a particle size distribution of
27 100% through 40 mesh, 60% through 100 mesh and 20
28 through 200 mesh. Type S typically will have a
29 particle size distribution of 100% through 40 mesh, 90%
30 through 100 mesh and 60% through 200 mesh. Mixtures of
31 the two types may be conveniently employed to provide
32 particulates having physical characteristics that are

1 suitable for various applications, as may be determined
2 by those skilled in the art of pharmaceutical
3 formulation, tableting and manufacturing.

4
5 The calcium hydrogen phosphate has low friability,
6 demonstrating a tensile strength of up to about 130
7 Kg/cm² when subjected to compressive forces of up to
8 3000 Kg/cm². The hardness of the tableted material
9 tends not to plateau at compression forces to that
10 limit, while materials such as microcrystalline
11 cellulose (Avicel PH 301), lactose, DI-TAB and Kyowa GS
12 tend to plateau at or about 700-1500 Kg/cm². The angle
13 of repose for the preferred materials typically is on
14 the order of 32-35 degrees.

15
16 Another material that may be utilized is that formed of
17 magnesium aluminometasilicate which may be represented
18 by the general formula



19
20 wherein n satisfies the relationship $0 \leq n \leq 10$.

21 Commercially available magnesium aluminometasilicates
22 are sold as Grades S₁, SG₁, UFL₂, US₂, FH₁, FH₂, FL₁, FL₂,
23 S₂, SG₂, NFL₂N, and NS₂N, under the trademark NeusilinTM
24 by Fuji Chemical Industries (U.S.A.) Inc., Englewood,
25 New Jersey. Especially preferred grades are S₁, SG₁,
26 US₂ and UFL₂. The most preferred for many applications
27 is grade US₂. Those materials, which are amorphous,
28 typically have a specific surface area (ar_{ca}) of about
29 100-300 m²/g, an oil absorption capacity of about 1.3-
30 3.4 ml/g, a mean particle size of about 1-2 microns, an
31 angle of repose about 25° -45°, a specific gravity of

1 about 2 g/ml and a specific volume of about 2.1-12
2 ml/g.

3
4 Other materials having similar physical characteristics
5 to the foregoing ranges for FujiCalin and Neusilin may
6 be equivalently substituted for the foregoing, as may
7 blends of the various materials described.

8
9 The liquid, active agent formulation may be in any form
10 that can be dispensed from the inside of the pores 4 as
11 the tablet disintegrates in the environment of use.
12 The formulation, for example, may be neat, liquid
13 active agent, liquid active agent in a solution,
14 suspension, emulsion or self-emulsifying composition,
15 or the like, or a liposomal solution or solid
16 formulation, or solid active agent in solution,
17 suspension or slurry. Optionally other dosage-forming
18 ingredients, such as an anti-oxidant, a suspending
19 agent, a surface active agent, and the like may be
20 present in the liquid, active agent formulation. The
21 liquid, active agent formulation will be released in a
22 form most suitable to provide active agent to the site
23 of delivery in a state in which it may be rapidly
24 absorbed in the environment of use to provide its
25 beneficial action with minimum delay. An example of
26 the usefulness of the rapid release form of the present
27 invention is demonstrated by its use for the popular
28 drug sildenafil citrate, sold under the trademark
29 Viagra[®]. The marketed dosage form is indicated to
30 provide maximum plasma concentrations in a subject at ½
31 to 3 hours after administration. More rapid onset of
32 the beneficial effect of the active agent is desirable.

1 and may be provided with the dosage forms of this
2 invention. That aspect of the inventions is
3 advantageous, also, for the preparation of dosage forms
4 that contain active agents which are poorly soluble in
5 water, such as for example the pain relievers
6 acetaminophen and non-steroidal antiinflammatory agents
7 such as ketoprofen, ibuprofen and the like.

8
9 The tableted dosage form 1 may be manufactured in
10 accordance with conventional methods, such as by
11 tumbling the porous particles together with the liquid,
12 active agent formulation or spraying of the liquid,
13 active agent formulation onto the porous particles in a
14 fluidized bed to sorb the liquid, active agent
15 formulation into the porous particles, and then
16 tableting or encapsulating the particles to form a
17 unitary dosage form. Typically, the desired quantity
18 of porous powder is directly contacted with the desired
19 amount of liquid, active agent formulation and mixed in
20 a blender, such as a V-blender or the like. The wet
21 material may be granulated by passing it through sieves
22 of suitable size, e.g., 40-80 mesh. To the extent that
23 some of the liquid, active agent formulation remains on
24 the outside of the granules, the addition of a quickly,
25 dissolving absorbent material, such as sugars, for
26 example, lactose, glucose, fructose, mannitol, maltose,
27 and sorbitol, starches, for example, malodextrin,
28 modified starches and the like, may be added in amounts
29 of 0.1%-10% by weight to improve the ability of the
30 granulated powder to flow without affecting the
31 immediate release characteristics of the invention.
32 Additional excipients can include 0.5-10% by weight of

1 tablet disintegration aids to promote rapid
2 disintegration of the tablet in the fluid environment
3 of use. Disintegration aids include cross-linked
4 polyvinyl pyrrolidone, starch granules, purified
5 cellulose, alginates, chemically-modified starch such
6 as sodium starch glycolate, cross-linked sodium carboxy
7 methyl cellulose, bentonite, and ion exchange resins.
8 The granulated material may then be compacted in a
9 conventional tableting press, at pressures of 500-3000
10 kgf/cm². The tablets may be provided in capsule sizes
11 (000), (00), (0), (1), (2), (3), (4), and (5), or other
12 non-conventional sizes as appropriate. The largest
13 number represents the smallest size. The tablets may
14 also be manufactured in various shapes such as round,
15 triangular, oval, square, and the like. Optionally,
16 the tablets can be compressed with score marks
17 providing the option of dividing the unit dose into
18 subunits prior to administration. Tableting methods
19 and equipment are well known in the art, such as
20 described, for example, in Remington's Pharmaceutical
21 Sciences, Eighteenth Edition (1990), Mack Publishing
22 Company, Easton, Pennsylvania. Tablets may be coated
23 with a film coat in conventional manner to provide a
24 smooth surface and also mask objectional flavors that
25 certain active agents may exhibit.

26
27 Also, the liquid, active agent formulation absorbed
28 into the particles may be filled into gelatin capsules
29 in the form of a paste or semi-compressed composition
30 (such as by screw filling wherein the pitch of the
31 screw changes to compress the composition as it moves
32 to the capsule feeder) having a hardness less than that

1 of the tableted dosage form to eliminate the
2 compression, tableting step. The gelatin capsule may
3 be made conveniently in two parts, with one part (the
4 "cap") slipping over and capping the other part (the
5 "body"). The two parts completely surround and
6 capsulate the internal lumen that contains the liquid,
7 active agent formulation, which may contain, as
8 described above, useful additives. The two parts are
9 fitted together after the body is filled with a
10 preselected formulation. The assembly is done by
11 slipping or telescoping the cap section over the body
12 section, and optionally sealing the cap and body.
13 Since it may take some time for the gelatin capsule
14 wall to dissolve, the time for delivery of the active
15 agent to the environment of use may be delayed somewhat
16 as compared to the tableted dosage form. However, once
17 the capsule has been at least partially dissolved, the
18 liquid, active agent formulation will begin to be
19 delivered to the environment of use in the liquid state
20 and the advantages of the invention will be
21 forthcoming.

22

23 The tableted dosage form of liquid, active agent
24 formulation absorbed into particles or the composition
25 of porous particles containing the liquid, active agent
26 formulation may also be utilized as the active agent
27 formulation in associated delivery technologies, such
28 as for example, the Chronset[®] drug delivery system of
29 Alza Corporation, Palo Alto, California. Such systems
30 can be programmed to release the active agent
31 formulation, in this case the tableted dosage form or
32 the loaded porous particles at designated times and at

1 targeted absorption sites. That technology is
2 described in US Patents Nos. 5,110,597; 5,223,265;
3 5,312,390; 5,443,459; 5,417,682; 5,498,255; 5,531,736;
4 and 5,800,422, which are incorporated herein by
5 reference.

6
7 While the dosage forms of the present invention are
8 considered to be particularly advantageous for the
9 preparation of immediate-release dosage forms, they do
10 allow for the modification of the surface area of the
11 tablet or capsule by methods described in US Patent
12 5,534,263, which is incorporated herein by reference,
13 to provide controlled release of the active agent. In
14 such an aspect of the invention, a banded dosage form
15 may provide the onset of immediate relief due to the
16 exposed portions of the dosage form that are not
17 banded, and then delayed or sustained release of the
18 active agent from the portions of the dosage form that
19 are banded. The advantages of the delivery of a
20 liquid, active agent formulation are present in this
21 configuration of the dosage form as well.

22
23 The expression "active agent" as used herein, comprises
24 any active agent, therapeutic compound, drug or
25 composition that can be delivered as a component of a
26 liquid, active agent formulation. The term active
27 agent includes active agents for veterinary and human
28 applications, such as pharmaceutical drugs. The term
29 drug includes an active substance that produces a
30 desired effect, often beneficial or therapeutic in
31 animals, including warm-blooded mammals, humans and
32 primates; avians; household and farm animals;

1 laboratory animals; fishes; reptiles; and zoo animals.
2 The drug can be in various forms such as unchanged
3 molecules, molecular complexes, pharmacologically
4 acceptable salts such as hydrochloride, hydrobromide,
5 sulfate, laurate, palmitate, phosphate, nitrite,
6 nitrate, borate, acetate, maleate, tartrate, oleate,
7 salicylate, and the like. For acidic drugs, salts of
8 metals, amines, or organic cations, for example
9 quarternary ammonium can be used. Derivatives of
10 drugs, such as bases, ester, ether and amide can be
11 used.

12
13 The expression "liquid, active agent formulation" may
14 include neat, liquid active agent, or a solution,
15 suspension, slurry, emulsion, self-emulsifying
16 composition, liposomal solution, or other flowable
17 composition in which the active agent is present. The
18 liquid, active agent formulation may be a "solid" at
19 temperatures lower than the temperature of the
20 environment of use, such as body temperature of humans
21 or animals, but the solid should become a flowable,
22 liquid composition after administration or application.
23 The active agent may be accompanied by a binder,
24 antioxidant, pharmaceutically acceptable carrier,
25 permeation enhancer and the like. The amount of an
26 active agent in a dosage form generally is about 0.05
27 ng to 5 g or more, with individual dosage forms
28 comprising, for example, 25 ng, 1 mg, 5 mg, 10 mg, 25
29 mg, 100 mg, 250 mg, 500 mg, 750 mg, 1.0 g, 1.2 g, and
30 the like, of active agent. The system can be
31 administered once, twice or thrice daily, or more or
32 less often as required.

1
2 The active drug that can be delivered includes
3 inorganic and organic compounds without limitation,
4 including drugs that act on the peripheral nerves,
5 adrenergic receptors, cholinergic receptors, nervous
6 system, skeletal muscles, cardiovascular system, smooth
7 muscles, blood circulatory system, synaptic sites,
8 neuroeffector junctional sites, endocrine system,
9 hormone systems, immunological system, organ systems,
10 reproductive system, skeletal system, autocrine systems,
11 alimentary and excretory systems, inhibitory of
12 autocrine and histamine systems, and physiological
13 systems. The active drug that can be delivered for
14 acting on these animal systems includes depressants,
15 beta-blockers, hypnotics, sedatives, psychic
16 energizers, tranquilizers, anti-convulsants, muscle
17 relaxants, steroids, antiparkinson agents, analgesics,
18 anti-inflammatories, polypeptides, local anesthetics,
19 muscle contractants, anti-microbials, anti-malarials,
20 hormonal agents, contraceptives, sympathomimetics,
21 diuretics, anti-parasitics, neoplastics, hypoglycemics,
22 ophthalmics, electrolytes, diagnostic agents,
23 cardiovascular drugs, calcium channel blockers,
24 angiotensin-converting enzyme inhibitors, and the like.

25
26 Exemplary drugs that can be delivered by the immediate-
27 release system of this invention include
28 prochlorperazine edisylate, ferrous sulfate,
29 aminocaproic acid, potassium chloride, mecamylamine
30 hydrochloride, procainamide hydrochloride, amphetamine
31 sulfate, benzphetamine hydrochloride, isoproterenol
32 sulfate, methamphetamine hydrochloride, phenmetrazine

1 hydrochloride, bethanechol chloride, metacholine
2 chloride, pilocarpine hydrochloride, atropine sulfate,
3 methascopolamine bromide, isopropamide iodide,
4 tridihexethyl chloride, phenformin hydrochloride,
5 methylphenidate hydrochloride, oxprenolol
6 hydrochloride, metoprolol tartrate, cimetidine
7 hydrochloride, diphenidol, meclizine hydrochloride,
8 prochlorperazine maleate, phenoxybenzamine,
9 thiethylperazine, maleate, anisindone, diphenadione
10 erythrityl terantrate, digoxin, isofurophate,
11 reserpine, acetazolamide, methazolamide,
12 bendroflumethiazide, chlorpropamide, tolazamide,
13 chlormadinone acetate, phenaglycodol, allopurinol,
14 aluminum aspirin, methotrexate, acetyl sulfisoxazole,
15 erythromycin, progestins, estrogenic progestational,
16 corticosteroids, hydrocortisone, hydrocorticosterone
17 acetate, cortisone acetate, triamcinolone,
18 methyltestosterone, 17 β -estradiol, ethinyl estradiol,
19 ethinyl estradiol 3-methyl ether, prednisolone, 17-
20 hydroxyprogesterone acetate, 19-nor-progesterone,
21 norgestrel, orethindone, norethiderone, progesterone,
22 norgestrone, norethynodrel, aspirin, indomethacin,
23 naproxen, fenoprofen, sulindac, diclofenac, indoprofen,
24 nitroglycerin, propranolol, metoprolol, valproate,
25 oxprenolol, timolol, atenolol, alprenolol, cimetidine,
26 clonidine, imipramine, levodopa, chloropropmazine,
27 reserpine, methyl dopa, dihydroxyphenylalanine,
28 pivaloyloxyethyl ester of α -methyl dopa hydrochloride,
29 theophylline, calcium gluconate ferrous lactate,
30 ketoprofen, ibuprofen, cephalixin, erythromycin,
31 haloperidol, zomepirac, sildenafil citrate, vincamine,
32 diazepam, phenoxybenzamine, β -blocking agents, calcium-

1 channel blocking drugs such as nifedipine, diltiazem,
2 verapamil, lisinopril, captopril, ramipril, fosinopril,
3 benazepril, libenzapril, cilazapril cilazaprilat,
4 perindopril, zofenopril, enalapril, indalapril,
5 gumapril, and the like. Other active agents are known
6 to the dispensing art as described in Pharmaceutical
7 Sciences, by Remington, 14th Ed., 1979, published by
8 Mack Publishing Co., Easton, Pa.; The Drug, The Nurse,
9 The Patient, Including Current Drug Handbook, 1976, by
10 Falconer et al., published by Saunder Company,
11 Philadelphia, Pa.; Medical Chemistry, 3rd Ed., Vol. 1
12 and 2, by Burger, published by Wiley-Interscience, New
13 York; and, Physician's Desk Reference, 55th Ed., 1998,
14 published by Medical Economics Co., New Jersey.
15 Particularly suited for the immediate-release dosage
16 form of this invention are pain relievers which are
17 sparingly soluble in water such as acetaminophen,
18 ibuprofen and ketoprofen.

19
20 The pharmaceutically acceptable carriers useful for
21 mixing with a drug to provide a dispensable
22 formulation, in a presently preferred embodiment, are
23 carriers that are compatible with the active agent and
24 which are easily excreted, metabolized, assimilated, or
25 the like by a warm-blooded animal. The carrier medium
26 used for the present purpose can be inorganic, or
27 organic, and of naturally occurring or synthetic
28 origin. Examples of carriers included in the term are
29 substances such as solutions, suspensions, liquids,
30 immiscible liquids, emulsions, sols, colloids, and
31 oils. Representative carriers include citrate esters
32 such as triethyl citrate, acetyl triethyl citrate,

1 tributyl citrate, trihexyl citrate, acetyl trihexyl
2 citrate, trioctyl citrate, acetyl trioctyl citrate,
3 acetin, diacetin, triacetin, glycerin, propylene
4 glycol, Vitamin E, triglycerides, liquid alkylene
5 glycols such as ethylene glycol, diethylene glycol,
6 triethylene glycol, ethylene glycol monomethyl ether,
7 liquid polyethylene glycols having a molecular weight
8 of 200, 300, 400 and higher; oils of plant, animal and
9 marine origin such as corn oil, almond oil, babassu
10 oil, eucalyptus oil, cottonseed oil, palm oil, peanut
11 oil, wheat germ oil, tung oil, mint oil, whale oil,
12 herring oil, mineral oil, and the like: emulsions of
13 castor oil in aqueous solutions of pigskin gelatin:
14 emulsions of gum arabic, water and ethyl cellulose;
15 liquid glyceryl triesters of a low molecular weight
16 fatty acids, particularly medium chain mono-, di-, and
17 tri-glycerides; oils with emulsifiers such as mono-or
18 di-glyceride of a fatty acid; a mixture of from about
19 70% to about 99.9% propylene glycol and from about 0.1%
20 to 30% of glycerin: a mixture of from about 70% to
21 about 99.9% propylene glycol and from about 0.1 to 30%
22 of ethanol; a mixture by volume of from about 80% to
23 99.9% of propylene glycol and from about 0.1% to about
24 20% of a mixture of from about 50% to 99.9% of ethanol
25 or glycerin and from 0.1% to about 50% of sterile
26 water; 5% dextrose in physiological saline; oils mixed
27 with surfactants such as poly-oxyethylene sorbitan
28 monolaurate; a mixture of peanut oil and beeswax;
29 peanut oil containing pectin; glycerine and gelatin,
30 with or without added water; glycerin/castile soap
31 formulation; distilled monoglycerides, distilled
32 propylene glycol monoesters, succinylated

1 monoglycerides, acetylated monoglycerides, glyceryl
2 monostearates, monoglycerides water-in-oil emulsions,
3 hydrogenated palm oil, hydrogenated palm oil stearine,
4 hydrogenated soybean oil, hydrogenated vegetable oil,
5 hydrogenated cottonseed oil, partially hydrogenated
6 oils, cottonseed oil, sunflower oil, grapeseed oil, and
7 the like Preferred liquid carriers generally are those
8 in which the unit dose of active agent is soluble.

9
10 In general, the present invention has particular
11 utility in the delivery of liquid, active agent
12 formulations that are in the form of emulsions or self-
13 emulsifying compositions. The term emulsion as used in
14 this specification denotes a two-phase system in which
15 one phase is finely dispersed in the other phase. The
16 term emulsifier, as used by this invention, denotes an
17 agent that can reduce and/or eliminate the surface and
18 the interfacial tension in a two-phase system. The
19 emulsifier agent, as used herein, denotes an agent
20 possessing both hydrophilic and lipophilic groups in
21 the emulsifier agent. The term microemulsion, as used
22 herein, denotes a multicomponent system that exhibits a
23 homogenous single phase in which quantities of a drug
24 can be solubilized. Typically, a microemulsion can be
25 recognized and distinguished from ordinary emulsions in
26 that the microemulsion is more stable and usually
27 substantially transparent. The term solution, as used
28 herein, indicates a chemically and physically
29 homogenous mixture of two or more substances.

30
31 The emulsion formulations of active agent generally
32 comprise 0.5 wt % to 99 wt % of a surfactant. The

1 surfactant functions to prevent aggregation, reduce
2 interfacial tension between constituents, enhance the
3 free-flow of constituents, and lessen the incidence of
4 constituent retention in the dosage form. The
5 therapeutic emulsion formulations useful in this
6 invention may comprise a surfactant that imparts
7 emulsification comprising a member selected from the
8 group consisting of polyoxyethylenated castor oil
9 comprising 9 moles of ethylene oxide,
10 polyoxyethylenated castor oil comprising 15 moles of
11 ethylene oxide, polyoxyethylenated castor oil
12 comprising 20 moles of ethylene oxide,
13 polyoxyethylenated castor oil comprising 25 moles of
14 ethylene oxide, polyoxyethylenated castor oil
15 comprising 40 moles of ethylene oxide, polyoxylenated
16 castor oil comprising 52 moles of ethylene oxide,
17 polyoxyethylenated sorbitan monopalmitate comprising 20
18 moles of ethylene oxide, polyoxyethylenated sorbitan
19 mono-oleate comprising 20 moles of ethylene oxide,
20 polyoxyethylenated sorbitan monolaurate comprising 20
21 moles of ethylene oxide, polyoxyethylenated sorbitan
22 monostearate comprising 20 moles of ethylene oxide,
23 polyoxyethylenated sorbitan monostearate comprising 4
24 moles of ethylene oxide, polyoxyethylenated sorbitan
25 tristearate comprising 20 moles of ethylene oxide,
26 polyoxyethylenated sorbitan monostearate comprising 20
27 moles of ethylene oxide, polyoxyethylenated sorbitan
28 trioleate comprising 20 moles of ethylene oxide,
29 polyoxyethylenated stearic acid comprising 8 moles of
30 ethylene oxide, polyoxyethylene lauryl ether,
31 polyoxyethylenated stearic acid comprising 40 moles of
32 ethylene oxide, polyoxyethylenated stearic acid

1 comprising 50 moles of ethylene oxide,
2 polyoxyethylenated stearyl alcohol comprising 2 moles
3 of ethylene oxide, and polyoxyethylenated oleyl alcohol
4 comprising 2 moles of ethylene oxide. The surfactants
5 are available from Atlas Chemical Industries,
6 Wilmington, Delaware; Drew Chemical Corp., Boonton, New
7 Jersey; and GAF Corp., New York, New York.

8
9 Typically, an active agent emulsified formulation
10 useful in the invention initially comprises an oil
11 phase. The oil phase of the emulsion comprises any
12 pharmaceutically acceptable oil which is not miscible
13 with water. The oil can be an edible liquid such as a
14 non-polar ester of an unsaturated fatty acid,
15 derivatives of such esters, or mixtures of such esters
16 can be utilized for this purpose. The oil can be
17 vegetable, mineral, animal or marine in origin.
18 Examples of non-toxic oils comprise a member selected
19 from the group consisting of peanut oil, cottonseed
20 oil, sesame oil, olive oil, corn oil, almond oil,
21 mineral oil, castor oil, coconut oil, palm oil, cocoa
22 butter, safflower, a mixture of mono- and di-
23 glycerides of 16 to 18 carbon atoms, unsaturated fatty
24 acids, fractionated triglycerides derived from coconut
25 oil, fractionated liquid triglycerides derived from
26 short chain 10 to 15 carbon atoms fatty acids,
27 acetylated monoglycerides, acetylated diglycerides,
28 acetylated triglycerides, olein known also as glycerol
29 trioleate, palmitin known as glyceryl tripalmitate,
30 stearin known also as glyceryl tristearate, lauric acid
31 hexylester, oleic acid oleylester, glycolyzed
32 ethoxylated glycerides of natural oils, branched fatty

1 acids with 13 molecules of ethyleneoxide, and oleic
2 acid decylester. The concentration of oil, or oil
3 derivative in the emulsion formulation is 1 wt % to 40
4 wt %, with the wt % of all constituents in the emulsion
5 preparation equal to 100 wt %. The oils are disclosed
6 in *Pharmaceutical Sciences* by Remington, 17th Ed., pp.
7 403-405, (1985) published by Mark Publishing Co., in
8 *Encyclopaedia of Chemistry*, by Van Nostrand Reinhold,
9 4th Ed., pp. 644-645, (1986) published by Van Nostrand
10 Reinhold Co.; and in U. S. Patent No. 4,259,323 issued
11 to Ranucci.

12
13 All dosage forms of the present invention may include
14 an antioxidant to slow or effectively stop the rate of
15 any autoxidizable material present in the dosage form,
16 particularly if it is in the form of a gelatin capsule.
17 Representative antioxidants comprise a member selected
18 from the group of ascorbic acid; alpha tocopherol;
19 ascorbyl palmitate; ascorbates; isoascorbates;
20 butylated hydroxyanisole; butylated hydroxytoluene;
21 nordihydroguaiaretic acid; esters of garlic acid
22 comprising at least 3 carbon atoms comprising a member
23 selected from the group consisting of propyl gallate,
24 octyl gallate, decyl gallate, decyl gallate; 6-ethoxy-
25 2,2,4-trimethyl-1,2-dihydro-guinoline; N-acetyl-2,6-di-
26 t-butyl-p-aminophenol; butyl tyrosine; 3-tertiarybutyl-
27 4-hydroxyanisole; 2-tertiary-butyl-4-hydroxyanisole; 4-
28 chloro-2,6-ditertiary butyl phenol; 2,6-ditertiary
29 butyl p-methoxy phenol; 2,6-ditertiary butyl-p-cresol;
30 polymeric antioxidants; trihydroxybutyro-phenone
31 physiologically acceptable salts of ascorbic acid,
32 erythorbic acid, and ascorbyl acetate; calcium

1 ascorbate; sodium ascorbate; sodium bisulfite; and the
2 like. The amount of antioxidant used for the present
3 purposes is about 0.001% to 25% of the total weight of
4 the composition present in the dosage form.

5 Antioxidants are known to the prior art in U.S. Pat.
6 Nos. 2,707,154; 3,573,936; 3,637,772; 4,038,434;
7 4,186,465 and 4,559,237.

8
9 All dosage forms of the present invention may also
10 contain a chelating agent to protect the active agent
11 either during storage or when in use. Examples of
12 chelating agents include, for example, polyacrylic
13 acid, citric acid, edetic acid, disodium edetic acid,
14 and the like. The chelating agent may be co-delivered
15 with the active agent in the environment of use to
16 preserve and protect the active agent *in situ*.
17 Protection is provided for active agents which are
18 inactivated by chelation with multivalent metal cations
19 such as calcium, magnesium or aluminum that may be
20 present in some foods and are at natural background
21 levels in the fluids of the gastrointestinal tract.
22 Such chelating agents may be combined with the liquid,
23 active agent formulation in the porous particles.

24
25 The liquid formulation of all forms of the present
26 invention may also comprise a surfactant or a mixture
27 of surfactants where the surfactant is selected from
28 the group consisting of nonionic, anionic and cationic
29 surfactants. Exemplary nontoxic, nonionic surfactants
30 suitable for forming a composition comprise alkylated
31 aryl polyether alcohols known as Triton®; polyethylene
32 glycol tertdodecyl throether available as Nonic®; fatty

1 and amide condensate or Alrosol[®]; aromatic polyglycol
2 ether condensate or Neutronyx[®]; fatty acid alkanolamine
3 or Ninol[®] sorbitan monolaurate or Span[®];
4 polyoxyethylene sorbitan esters or Tweens[®]; sorbitan
5 monolaurate polyoxyethylene or Tween 20[®]; sorbitan
6 mono-oleate polyoxyethylene or Tween 80[®]; triblock
7 copolymers polyoxyethylene-polyoxypropylene-
8 polyoxyethylene or Pluronic[®]; polyglycolized
9 glycerides such as Labraesol, polyoxyethylated castor
10 oil such as Cremophor and polyoxypropylene-
11 polyoxyethylene-8500 or Pluronic[®]. By way of example,
12 anionic surfactants comprise sulfonic acids and the
13 salts of sulfonated esters such as sodium lauryl
14 sulfate, sodium sulfoethyl oleate, dioctyl sodium
15 sulfosuccinate, cetyl sulfate sodium, myristyl sulfate
16 sodium; sulfated esters; sulfated amides; sulfated
17 alcohols; sulfated ethers; sulfated carboxylic acids;
18 sulfonated aromatic hydrocarbons; sulfonated ethers;
19 and the like. The cationic surface active agents
20 comprise cetyl pyridinium chloride; cetyl trimethyl
21 ammonium bromide; diethylmethyl cetyl ammonium
22 chloride; benzalkonium chloride; benzethonium chloride;
23 primary alkylammonium salts; secondary alkylammonium
24 salts; tertiary alkylammonium salts; quaternary
25 alkylammonium salts; acylated polyamines; salts of
26 heterocyclic amines; palmitoyl carnitine chloride,
27 behentriammonium methosulfate, and the like. Generally,
28 from 0.01 part to 1000 parts by weight of surfactant,
29 per 100 parts of active agent is admixed with the
30 active agent to provide the active agent formulation.

1 Surfactants are known to the prior art in U.S. Pat.
2 Nos. 2,805,977; and in 4,182,330.

3
4 The liquid formulation of all forms of the present
5 invention may also comprise permeation enhancers that
6 facilitate absorption of the active agent in the
7 environment of use. Such enhancers may, for example,
8 open the so-called "tight junctions" in the
9 gastrointestinal tract or modify the effect of cellular
10 components, such as p-glycoprotein and the like.
11 Suitable enhancers include alkali metal salts of
12 salicyclic acid, such as sodium salicylate, caprylic or
13 capric acid, such as sodium caprylate or sodium
14 caprate, and the like. Enhancers may include the bile
15 salts, such as sodium deoxycholate. Various p-
16 glycoprotein modulators are described in US Patents
17 5,112,817 and 5,643,909, which are incorporated herein
18 by reference. Various other absorption enhancing
19 compounds and materials are described in US Patent
20 5,824,638, which also is incorporated herein by
21 reference. Enhancers may be used either alone or as
22 mixtures in combination with other enhancers.

23
24 The liquid, active agent formulation of all dosage
25 forms of the present invention may optionally be
26 formulated with inorganic or organic acids or salts of
27 drugs which promote dissolution and disintegration or
28 swelling of the porous particles upon contact with
29 biological fluids. The acids serve to lower the pH of
30 the microenvironment at the porous particle, and
31 promote rapid dissolution of a particle, such as
32 calcium hydrogen phosphate, that is soluble in low pH

1 environments, thus providing rapid liberation of the
2 liquid, active agent formulation contained in the
3 porous particle. Examples of organic acids include
4 citric acid, tartaric acid, succinic acid, malic acid,
5 fumaric acid and the like. Salts of drugs where the
6 anion of the salt is acidic, such as acetate,
7 hydrochloride, hydrobromide, sulfate, succinate,
8 citrate, and the like, can be utilized to produce
9 immediate disintegration and dissolution of the porous
10 particle. A more complete list of acidic components
11 for this application is provided in Journal of
12 Pharmaceutical Sciences, "Pharmaceutical Salts", Review
13 Articles, January, (1977), Vol. 66, No. 1, pages 1-19.
14 The interaction of an acidic component with a porous
15 particle of, for example, calcium hydrogen phosphate,
16 in the presence of water from gastric fluids
17 accelerates dissolution of the particle at a greater
18 rate than gastric fluid alone, producing a more rapid
19 and complete release of the liquid, active agent
20 formulation into the environment of use. Likewise
21 alkaline components or salts of drugs where the cation
22 of the salt is alkaline such as choline may be
23 incorporated into the liquid, active agent formulation
24 to promote rapid and complete dissolution of a porous
25 particle which is soluble or swells at elevated pH.
26 Such a particle may be formed, for example, of
27 poly(methacrylic acid-methyl methacrylate) 1:2
28 available commercially as Eudragit S100 (Rohm America,
29 Somerset, New Jersey.

30

31 The following examples are illustrative of the first
32 embodiment of the present invention.

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EXAMPLE 1

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A general procedure for the formation of the tableted form of the dosage form of the invention is presented below. Percentages are by weight unless otherwise specified.

An immediate-release dosage form of the anti-impotence drug sildenafil citrate is prepared. 70 Grams of the active agent sildenafil citrate is mixed with 280 grams of the liquid carrier propylene glycol. The active agent/liquid mixture is added to 550 grams of calcium hydrogen phosphate particles, FujiCalin® Type S. The blend is tumble mixed at room temperature in a twin-shell blender for 20 minutes, producing a free-flowing dry mix. Then 100 grams of the disintegrating agent low-substituted hydroxypropyl cellulose, having an average hydroxypropoxyl content of 10-13 weight percent is added to the blend, and the combined mixture is tumble mixed for an additional 5 minutes. The resulting formulation is transferred to a tablet press. Oval tablets having a major axis length of $\frac{1}{2}$ inch (121.7 mm) and a minor axis length of $\frac{9}{32}$ inch (7.1mm) and weighing 357 mg are compressed using a force of 1.0 ton. Each tablet contains a unit dose of 25 mg of active agent. The tablets are transferred to a pharmaceutical pan coater where 20 mg of water-soluble film coating is applied to each tablet. The composition of the film coating consists of 75 parts hydroxypropyl methylcellulose and 25 parts polyethylene glycol. The hydroxypropyl methylcellulose has a hydroxyl content of 10 weight percent, a methoxyl

1 content of 29 weight percent, and molecular weight of
2 approximately 11,900 grams per mole. The polyethylene
3 glycol has a molecular weight of 8,000 grams per mole.
4 The resulting tablet disintegrates rapidly when placed
5 in a simulated gastric fluid environment and release
6 active agent immediately.

7

8 EXAMPLE 2

9 The general procedure of EXAMPLE 1 is followed to
10 prepare dosage forms containing 250 mg of
11 acetaminophen, 50 and 100 mg of ibuprofen and 25, 50
12 and 75 mg of ketoprofen in a tablet form. The
13 fabricated dosage forms disintegrate rapidly when
14 placed in a simulated gastric fluid environment and
15 release active agent immediately.

16

17 EXAMPLE 3

18 Blends of 80% calcium hydrogen phosphate particles,
19 FujiCalin® Type S, and 20% magnesium aluminosilicate
20 powder, Neusilin™ grades S₁, SG₁, US₂ and UFL₂,
21 respectively, are substituted for the 100% FujiCalin®
22 Type S particles of EXAMPLE 1, and unit dosage forms
23 containing 25 mg of sildenafil citrate, 250 mg of
24 acetaminophen, 50 and 100 mg of ibuprofen and 25, 50
25 and 75 mg of ketoprofen in tablet form are prepared.
26 The fabricated dosage forms disintegrate rapidly when
27 placed in a simulated gastric fluid environment and
28 release active agent immediately.

29

30 EXAMPLE 4

31 Proportional amounts of magnesium aluminosilicate
32 powder, Neusilin™ grades S₁, SG₁, US₂ and UFL₂,

1 respectively, are substituted for the 100% FujiCalin[®]
2 Type S particles of EXAMPLE 1, and unit dosage forms
3 containing 25 mg of sildenafil citrate, 250 mg of
4 acetaminophen, 50 and 100 mg of ibuprofen and 25, 50
5 and 75 mg of ketoprofen in tablet form are prepared.
6 The fabricated dosage forms disintegrate rapidly when
7 placed in a simulated gastric fluid environment and
8 release active agent immediately.

9

10

EXAMPLE 5

11 An equivalent amount of FujiCalin[®] Type SG particles is
12 substituted for the FujiCalin[®] Type S particles in
13 EXAMPLE 1, and the procedures of that example are
14 generally followed to prepare unit dosage forms
15 containing 25 mg of sildenafil citrate, 250 mg of
16 acetaminophen, 50 and 100 mg of ibuprofen and 25, 50
17 and 75 mg of ketoprofen in tablet form. The fabricated
18 dosage forms disintegrate rapidly when placed in a
19 simulated gastric fluid environment and release active
20 agent immediately.

21

22 Figures 2-5 depict forms of a delivery device according
23 to the second embodiment of the present invention using
24 a bioerodible carrier. The delivery device or active
25 agent dosage form 10 comprises a polymer matrix 11
26 having a plurality of porous particles 12 having pores
27 13 in which the liquid, active agent 14 is absorbed
28 (illustrated by the multitude of dots) dissolved or
29 dispersed therein. Polymer matrix 11 typically is
30 formed of combination of a swellable, high molecular
31 weight, water-soluble polymer and a hydroattractant.

32

1 Materials useful for sorbing the liquid active agent
2 formulations have already been described herein.
3 Generally, the polymer/liquid, active agent formulation
4 matrix will contain at least 10% of the polymer
5 component to form a gel when in the environment of use.
6

7 Particular suitable porous particle is exemplified by
8 the particular forms of calcium hydrogen phosphate and
9 magnesium aluminometasilicate as previously described.
10 Other absorptive materials may be substituted for the
11 foregoing. For example, powders of microcrystalline
12 cellulose sold under the tradenames Avicel (FMC
13 Corporation) and Elcema (Degussa) and porous
14 agglomerated silicon dioxide, sold under the tradenames
15 Cab-O-Sil (Cabot) and Aerosil (Degussa), may be used.
16

17 The method of this form of the invention may be applied
18 generally to liquid formulations such as those sold
19 commercially as liquid formulations or those prepared
20 as described herein. Examples of commercially
21 available encapsulated liquid formulations that may be
22 utilized include, inter alia, Placidyl[®] brand of
23 ethchlorvynol, Adalat[®] brand of nifedipine, VePesid[®]
24 brand of etoposide, Lanoxicaps[®] brand of digoxin,
25 Zantac[®] brand of ranitidine hydrochloride, Sandimmune[®]
26 and Neoral[®] brands of cyclosporin, Calderol[®] brand of
27 calcifediol, Zarontin[®] brand of ethosuximide,
28 Procardia[®] brand of nifedipine, Rocaltrol[®] brand of
29 calcitriol and Vescenoid[®] brand of tretinoin.
30

1 Representative examples of the swellable polymer
2 comprising high molecular weight, water-soluble
3 polymers are polyethylene oxide and cellulosic polymer
4 derivatives including hydroxypropyl cellulose,
5 hydroxypropyl methyl cellulose, hydroxyethyl cellulose,
6 sodium carboxy methylcellulose, calcium carboxymethyl
7 cellulose, methyl cellulose, as well as noncellulosics
8 such as maltodextrin, polyvinyls, polyvinyl alcohol,
9 polyacrylic acids, alginates, gelatin, natural gums,
10 including guar, lightly crosslinked versions of these
11 polymers, starches, starch graft copolymers and the
12 like. The polymers generally have number average
13 molecular weights over 50,000 grams per mole, such as
14 between 50,000 and 10,000,000 grams per mole and
15 representative viscosities, e.g. for polyethylene oxide
16 in the range of 12-20,000 cps (5% aq, 25°C, MW 100,000-
17 900,000), 400-4000 cps (2% aq, 25°C, MW 1,000,000 -
18 2,000,000) and 1500-15,000 cps (1% aq, 25°C, MW
19 4,000,000 - 8,000,000) [Brookfield viscometer,
20 rotational spindle]; for methylcellulose in the range
21 of 1,500-18,000 cps (2% aq, 20°C, MW 62,000-134,000)
22 [Ubbelohde tube viscometer]; for hydroxypropyl
23 methylcellulose in the range of 4,000-100,000 cps (2%
24 aq, 20°C, MW 88,000-242,000) [Ubbelohde tube
25 viscometer]; for hydroxyethyl cellulose in the range of
26 75-400 cps (5% aq, 25°C, MW 90,000-200,000), 400-6500
27 cps (2% aq, 25°C, MW 300,000 - 720,000) and 1500-5,000
28 cps (1% aq, 25°C, MW 1,000,000 - 1,300,000) [Brookfield
29 viscometer, rotational spindle]; for guar about 5100
30 cps (1%) [Brookfield viscometer, rotational spindle];
31 for poly(methyl vinyl ether/maleic anhydride) in the

1 range of 15 to greater than 200 cps (5% aq., MW 20,000-
2 80,000) [Brookfield viscometer, rotational spindle];
3 for polyvinyl alcohol in the range 27-65 cps (4%aq, 20°C
4 [Hoeppler falling ball method and 1100-1500 cps (10%aq,
5 25°C) [Brookfield viscometer, rotational spindle; for
6 sodium carboxymethyl cellulose in the range of 25-50
7 cps (2% aq, 25°C) (MW 90,000) to about 2,500-6,000 cps
8 (1% aq, 25°C) (MW 700,000) [Brookfield viscometer,
9 rotational spindle]; and for sodium polyacrylic acid
10 5000-80,000 (0.5% aq) (MW 750,000 - 4,000,000)
11 [Brookfield viscometer, rotational spindle]. Polymers
12 having molecular weights between 300,000 and 8,000 000
13 grams per mole are preferred, and those having
14 molecular weights between about 2,000,000 to 8,000,000
15 grams per mole are especially preferred. Polyethylene
16 oxide having a number average molecular weight between
17 about 5,000,000 to 8,000,000 grams per mole is most
18 especially preferred, e.g. Polyox 303 and Polyox 308.
19 Also, especially preferred are methylcellulose
20 type/grade A15C, A4M, A18M and hydroxypropyl
21 methylcellulose type/grade K4M, K15M, K100M, E4M and
22 F4M (Dow Chemical Company); hydroxyethyl cellulose such
23 as Natrosol® HEC; hydroxypropyl cellulose such as
24 Klucel (Grades H, M, G, J, L, E - Aqualon Company);
25 guar such as Supercol® Guar U (Aqualon Company); pectin
26 such as GENU Pectin (Aqualon Company); carrageenan such
27 as GENU Carrageenan (Aqualon Company); poly(methyl
28 vinyl ether/maleic anhydride) such as Gantrez® AN
29 Copolymer (AN-119, -139, -149, -169, -179, GAF
30 Corporation); polyvinyl alcohol such as Elvanol® 71-30,

1 Elvanol[®] 85-30, Elvanol[®] 50-42 and Elvanol[®] HV (DuPont);
2 sodium carboxymethyl cellulose such as Aqualon
3 cellulose gum grade 7H4; polyacrylic acids such as
4 Carpobol[®] resin grades 971P, 974P, 980, 981, 1382,
5 2984, 5984, ETD 2001, ETD 2050, calcium polyacrylic
6 acids such as Noveon[®] resin grades AA-1, CA-1 and CY-2,
7 and sodium polyacrylic acid (BF Goodrich, Cleveland,
8 Ohio).

9
10 Representative examples of hydroattractants are water-
11 insoluble polymers such as low substituted
12 hydroxypropyl cellulose, microcrystalline cellulose
13 (Avicel), cross-linked sodium or calcium carboxymethyl
14 cellulose, cellulose fiber (Solka-Floc or Elcema),
15 cross-linked polyvinyl pyrrolidone (Polyplasdone XL),
16 cross-linked Amberlite resin, alginates (Satialgine),
17 colloidal magnesium-aluminum silicate (Veegum), corn
18 starch granules, rice starch granules, potato starch
19 granules, wheat starch granules, sodium carboxymethyl
20 starch (Expotab, Primojel), corn
21 starch/acrylamide/sodium acrylate copolymer,
22 acrylamide/sodium acrylate copolymer and the like. A
23 particularly suitable hydroattractant is hydroxypropyl
24 cellulose having a hydroxypropyl content of between
25 about 8-15 weight percent, and preferably about 10-13
26 weight percent, such as that supplied as Low
27 Substituted Hydroxypropyl Cellulose grade 11 as
28 manufactured by Shin-Etsu Chemical Company, Ltd.,
29 Tokyo, Japan.

30

31 Typically, the water soluble, high molecular weight
32 polymer in the polymer matrix is present in from about

1 5% to about 90% by weight based on the total weight of
2 the active agent formulation matrix, and the
3 hydroattractant is present in from about 5% to about
4 70% by weight based on the total weight of the active
5 agent formulation matrix. The particular percentages
6 may be chosen to provide the desired retention time in
7 the stomach and the desired release profile of active
8 agent. However, it is presently preferred to have the
9 polymer matrix contain from about 10 weight percent to
10 about 50 weight percent of the water soluble, high
11 molecular weight polymer and from about 10 weight
12 percent to about 60 weight percent of the
13 hydroattractant, with weight percentages of water
14 soluble, high molecular weight polymer in the range of
15 10 to 40 weight percent and hydroattractant in the
16 range of 25 to 35 being especially preferred.

17
18 Dosage form 10 is conveniently cylindrically shaped
19 with rounded ends that facilitate administration of the
20 dosage form in its non-swelled state. In FIG. 2A, the
21 device 10 is shown in preparation prior to application
22 of the insoluble material or band 15 shown in FIG. 2B.
23 The insoluble material exemplified as band 15,
24 circumscribes a portion of the outer surface of the
25 polymer matrix 11. While a single band is illustrated
26 in FIG. 2, additional bands such as illustrated in FIG.
27 5 can be utilized depending on the particular
28 application for which the device is being used.

29
30 The band of insoluble material 15 is applied to the
31 outer surface of the polymer matrix. The insoluble
32 material imparts rigidity to the gel-forming polymer

1 matrix to manage gastric retention time and further
2 control the delivery profile of the active agent of
3 interest. Band 15 typically exhibits low water
4 permeability and will prevent that portion of the
5 polymer matrix which it surrounds from imbibing fluid,
6 thus substantially limiting any swelling of polymer
7 matrix 11 at that location. The number, size, and
8 placement of the insoluble bands that are applied onto
9 the surface of the active agent formulation matrix may
10 be varied to adjust the active agent delivery profile
11 and the retention time in the stomach. For example,
12 bands 0.1 mm to about 12 mm in width, preferably
13 between about 0.5 and 8 mm, may be applied onto the
14 active agent formulation matrix surface. Further,
15 between about 1 and 10 bands may be used, but generally
16 between about 1 and 3 are affixed to the matrix. The
17 bands may be placed close together (i.e., within about
18 0.5 mm of each other) or may be placed about 8 to 12 mm
19 apart.

20
21 With reference to Figs. 5A-5D, dosage form 10 is formed
22 with two bands 15, each circumscribing a portion of the
23 surface of polymer matrix 11 in which active agent (not
24 shown) is dispersed. FIG. 5A illustrates dosage form
25 10 in its initial configuration before it has imbibed
26 any fluid. Upon administration to a subject, dosage
27 form 10 swells as shown in FIG. 5B in those segments of
28 polymer matrix 11 that are not surrounded by bands 15.
29 Because of the low fluid impermeability of bands 15,
30 those portions of polymer matrix 11 surrounded by bands
31 15 do not appreciably imbibe fluid and the polymer in
32 such segments of the polymer matrix does not swell to

1 any significant extent. FIGs. 5C and 5D illustrate
2 sequential states of dosage form 10 after it is
3 substantially eroded by gastric fluid and contractions
4 of the stomach. Eventually, dosage form 10 will
5 separate into two pieces and be expelled from the
6 stomach.

7
8 The insoluble material comprising band(s) 15 may be any
9 material that is nontoxic, biologically inert,
10 nonallergenic and nonirritating to body tissue, that
11 exhibits little impermeability to liquids, and that
12 maintains its physical and chemical integrity in the
13 environment of use for at least a portion of the
14 dispensing period. The low liquid permeability of the
15 insoluble material serves to limit swelling of the
16 polymer matrix in that section of the polymer matrix
17 that is surrounded by the band.

18
19 Insoluble materials from which the bands may be
20 prepared include, for example, polyethylene,
21 polystyrene, ethylene-vinyl acetate copolymers,
22 polycaprolactone and Hytrel[®] polyester elastomers (Du
23 Pont). Additional banding materials include but are
24 not limited to polysaccharides, cellulosics, cellulose
25 acetate, cellulose acetate propionate, cellulose
26 acetate butyrate, cellulose acetate pseudolatex (such
27 as described in U.S. Patents 4,931,285 and 5,024,842),
28 cellulose acetate propionate, cellulose acetate
29 butyrate, ethyl cellulose, ethyl cellulose pseudolatex
30 (such as Surelease[®] as supplied by Colorcon, West
31 Point, PA or Aquacoat[™] as supplied by FMC Corporation,
32 Philadelphia, PA), nitrocellulose, polylactic acid,

1 poly- glycolic acid, polylactide glycolide copolymers,
2 polycaprolactone, polyvinyl alcohol, polyvinyl acetate,
3 polyethylene vinylacetate, polyethylene teraphthalate,
4 polybutadiene styrene, polyisobutylene, polyisobutylene
5 isoprene copolymer, polyvinyl chloride, polyvinylidene
6 chloride-vinyl chloride copolymer, copolymers of
7 acrylic acid and methacrylic acid esters, copolymers of
8 methylmethacrylate and ethylacrylate, latex of acrylate
9 esters (such as Eudragit[®] supplied by RöhmPharma,
10 Weiterstadt, Germany), polypropylene, copolymers of
11 propylene oxide and ethylene oxide, propylene oxide
12 ethylene oxide block copolymers, ethylenevinyl alcohol
13 copolymer, poly sulfone, ethylene vinylalcohol
14 copolymer, polyxylylenes, polyamides, rubbers, such as
15 styrenebutadiene, polyisobutylene and the like, natural
16 and synthetic waxes, paraffin, carnauba wax, petroleum
17 wax, white or yellow bees wax, castor wax, candelilla
18 wax, rice bran wax, microcrystalline wax, stearyl
19 alcohol, cetyl alcohol, bleached shellac, esterified
20 shellac, chitin, chitosan, silicas, polyalkoxysilanes,
21 polydimethyl siloxane, polyethylene glycol-silicone
22 elastomers, crosslinked gelatin, zein, electromagnetic
23 irradiation crosslinked acrylics, silicones, or
24 polyesters, thermally crosslinked acrylics, silicones,
25 or polyesters, butadiene-styrene rubber, glycerol ester
26 of partially dimerized rosin, glycerol ester of
27 partially hydrogenated wood rosin, glycerol ester of
28 tall oil rosin, glycerol ester of wood rosin,
29 pentaerythritol ester of partially hydrogenated wood
30 rosin, pentaerythritol ester of wood rosin, natural or
31 synthetic terpene resin and blends of the above.
32

1 The banding materials often are also formulated with
2 plasticizers, and optionally with wetting agents,
3 surfactants, opacifiers, colorants, flavorants, taste-
4 masking agents, and the like. Examples of typical
5 plasticizers are as follows: triacetin, polyhydric
6 alcohols, polyethylene glycol, glycerol, propylene
7 glycol, acetate esters, glycerol triacetate, triethyl
8 citrate, acetyl triethyl citrate, glycerides,
9 acetylated monoglycerides, oils, mineral oil, castor
10 oil and the like. Referring again to the embodiment of
11 the invention depicted in FIG. 2A, the polymer matrix
12 11 in its non-swelled state has a length L1 and a
13 maximum diameter D1 intermediate the ends. FIG. 3
14 shows dispensing device 10 after having been placed in
15 the stomach. The active agent formulation matrix 11 on
16 each side of the band 15 has swelled from imbibing
17 fluid from the stomach and begun to erode, thereby
18 releasing porous particles 12 to the stomach
19 environment. In contrast to the exposed segments of
20 the swollen polymer matrix 11, band 15 and the portion
21 of the polymer matrix beneath it have not swelled to
22 such an extent. Accordingly, that segment of the
23 polymer matrix surrounded by band 15 is maintained in a
24 constrained and more compressed, non-swollen state than
25 the unbanded portion of the matrix. Since band 15 does
26 not take up an appreciable amount of fluid from the
27 stomach and swell, band 15 retains its substantially
28 rigid or semi-rigid form, and provides an element of
29 rigidity to the dosage form as a whole. While it is
30 not entirely clear how band 15 and the constrained
31 segment of polymer matrix 11 facilitate retention of
32 the dosage form in the stomach through housekeeping

1 waves, it is thought that the band reduces the rate of
2 erosion of the polymer matrix, thus maintaining a
3 larger effective size of the dosage form and reducing
4 the chance for its expulsion from the stomach, for a
5 longer period of time than would otherwise occur if the
6 band was not present. Additionally, the presence of
7 the band on the polymer matrix provides a semi-rigid
8 segment of the dosage form that appears to cause the
9 dosage form to be retropelled into the main area of the
10 stomach as a reaction to the stomach contractions
11 rather than being expelled by the housekeeping wave, as
12 a less rigid gel would be inclined to be.

13

14 After swelling, the dosage form 10 has a length L_2 and
15 a maximum diameter D_2 measured at the widest part of
16 the swollen polymer matrix. Generally, for human
17 applications the largest dimension of the device in the
18 swollen state equivalent to the diameter D_2 should be
19 greater than 7 mm, preferably 10 mm or greater, and
20 most preferably 13 mm or greater during the period of
21 residence in the stomach when active agent is being
22 dispensed. Since the dosage form is intended to remain
23 in the stomach for a prolonged retention period, the
24 effective diameter of the active agent dosage form in
25 when in its swollen state in the stomach may have to be
26 significantly larger than 13 mm, and may extend to more
27 than 50 mm or greater. Larger dosage forms may be
28 appropriate particularly when the polymer matrix is
29 designed to erode relatively rapidly over time in order
30 to provide the required delivery of active agent for
31 therapeutic effect. For applications in animals other

1 than humans, for example in dogs, the maximum diameter
2 should be greater than about 2 mm.

3
4 The maximum dimension for any particular dosage form
5 will depend on the particular application and animal in
6 which the device is being used. Such dimensions can be
7 determined by those skilled in the art in accordance
8 with the teaching herein and the various patents and
9 publications noted herein and existing in the related
10 art. A practical consideration, particularly for oral
11 administration to humans, is that the initial size of
12 the device be such that it can be reasonably,
13 comfortably swallowed. For human oral applications, a
14 preferred size of the device in its form prior to
15 administration to the stomach would be on the order of
16 a size 000 capsule to a size 5 capsule. However, it is
17 understood that smaller or larger sizes could be used
18 for particular applications where necessary.

19
20 Since the dosage forms of the invention may be gel-
21 forming, it may be desirable to wet the outer surface
22 of the dosage form immediately prior to the subject
23 swallowing the dosage form in order to provide a more
24 slippery outer surface and promote ease of swallowing.
25 Alternatively, the matrix core can be inserted into a
26 hard gelatin capsule prior to application of the band
27 in order to facilitate swallowing and also promote ease
28 of manufacture in applying and forming the bands. Upon
29 entering the stomach, that portion of the hard gelatin
30 capsule that is not covered by the band will dissolve,
31 exposing the polymer matrix to fluid in the stomach.
32 As the polymer matrix imbibes fluid, the dosage form

1 will swell in the exposed segments as previously
2 described. The dosage form typically is prepared to
3 allow for swelling at a controlled rate, particularly
4 at a limited initial rate, so that the dosage form does
5 not swell inordinately during the swallowing process
6 and result in obstruction of the esophagus.

7
8 It is preferred that the dosage forms of certain
9 embodiments be administered when the subject is in the
10 fed state to allow time for maximum swelling of the
11 polymer matrix prior to the housekeeping wave being
12 initiated. Generally a meal size that results in a
13 delay of the housekeeping wave of from about 1 to 3
14 hours is satisfactory. It may be preferable to
15 administer one or more of the dosage forms at the start
16 of each dosing period, depending on the size of the
17 dosage form, to facilitate swallowing and yet provide
18 sufficient dose of active agent. Particularly in those
19 instances where the dosage form is near the lower end
20 of the size range, i.e., the maximum diameter along the
21 longitudinal axis is on the order of 7-13 mm, it is
22 preferable that the dosage form be administered to the
23 subject in the fed state to allow for significant
24 swelling of the dosage form prior to the housekeeping
25 wave occurring. Typically, administration will occur
26 with the meal or within two hours thereafter, and
27 preferably within one hour of completion of the meal.
28 Depending on the half-life of an active agent, once-a-
29 day dosing could conveniently occur with or after
30 dinner. For b.i.d. (i.e., twice-a-day) dosing to a
31 human subject, the dosage form can conveniently be
32 administered with or after breakfast and dinner, but,

1 if after, preferably within one or two hours after
2 conclusion of the meal. For more frequent
3 administration, such as t.i.d., the dosage form may be
4 administered after breakfast, lunch and dinner. For
5 administration within usual meal patterns, it is
6 desirable that the subject consume small amounts of
7 food or liquids prior to administration of the dosage
8 form. The dosage form may be administered prior to the
9 taking of food if administered with a sufficient
10 quantity of liquid so as to delay onset of the
11 housekeeping wave, until consumption of food is
12 initiated.

13

14 To facilitate retention of the dosage forms of the
15 invention, particularly if the dosage form is to be
16 administered to a subject in the fasted state, it may
17 be desirable to combine one or more gastric-emptying
18 delaying agents with the active agent composition or
19 coat the dosage form with a composition containing a
20 gastric-emptying delaying agent, i.e., a substance that
21 delays onset of the housekeeping wave of the IMMC.

22 Examples of agents for delaying onset of the
23 housekeeping wave, preferably locally delivered by the
24 dosage form in amounts not resulting in any substantial
25 systemic effect to the subject, as for example,
26 anticholinergic agents such as propantheline, and other
27 agents including, but not limited to, methylcellulose,
28 guar gum, fats such as triglyceride esters, e.g.,
29 triethanol myristate, fatty acids of 10-15 carbon
30 atoms, and the like.

31

1 Figs. 4A and 4B show dosage form 10 after a length of
2 time in the fluid environment of the stomach. Polymer
3 matrix 11 has eroded at the exposed surface of the
4 matrix, i.e., those portions of the matrix not covered
5 by the insoluble material 15 to such an extent that the
6 device 10 is smaller than its initial swollen
7 configuration. Erosion of the matrix permits release
8 of the porous particles from the matrix. After the
9 porous particles are released, the liquid, active agent
10 may elute by diffusion or convection from the pores
11 into the environment of use. Additionally, as the
12 released porous particles disintegrate in the gastric
13 environment, the liquid, active agent formulation will
14 be directly released into the environment of use. At
15 some point, the matrix may erode to such an extent that
16 the remainder of the dosage form is expelled from the
17 stomach. Band 15 will be expelled from the stomach
18 either alone, if it has separated from the dosage form
19 at some time near the end of the delivery period, or as
20 part of the remainder of the dosage form expelled from
21 the stomach. In some applications, it may be desirable
22 to form band 15 with weakened portions so that band 15
23 splits and falls away from the polymer matrix after
24 some predetermined time in the stomach to permit a
25 particular release pattern of active agent from the
26 dosage form over the delivery period.

27
28 The dosage forms in this embodiment of the invention
29 can be prepared by standard methods from the materials
30 previously described. Typically, the liquid, active
31 agent formulation will be prepared independently of the
32 porous particle; although in some circumstances, it may

1 be desirable to combine the formation of the liquid,
2 active agent formulation with the mixing of the
3 formulation components and the porous particles. As
4 described previously, the liquid formulation may be a
5 solution, suspension, dispersion, emulsion, etc.
6 depending on the particular application for which the
7 dosage form is intended.

8
9 After, the liquid, formulation is prepared, the desired
10 quantity of liquid, active agent formulation and porous
11 particles may be mixed in a blender to sorb the liquid
12 into the porous particles. That mixture may be milled
13 by passing it through mesh screens to insure intimate
14 mixing and complete absorption of the liquid, active
15 agent formulation into the porous particles. The wet
16 granulation may then be dried at ambient conditions to
17 facilitate handling. However, the drying conditions
18 are not so severe as to evaporate a significant amount
19 of the liquid of the liquid, active formulation. Also,
20 to facilitate handling, it may be desirable to add a
21 small amount of another absorbent, such as a soluble
22 sugar, e.g., maltose or the like, that will readily
23 dissolve in the environment of use when the porous
24 particle is released from the dosage form, but not
25 subsequently change the desired release characteristics
26 of the dosage form. Small amounts of inert absorbents,
27 such as microcrystalline cellulose or silicon dioxide,
28 may be substituted for the soluble material, but,
29 again, the quantities should not be so great that the
30 desired release characteristics of the liquid, active
31 agent formulation from the absorbent particles is
32 significantly affected. Another method of manufacture

1 would be to sorb the liquid, active agent formulation
2 into the particles in a fluidized bed of the particles.
3 Those and other methods are conventional and will be
4 apparent to those skilled in the art.

5
6 An appropriate quantity of porous particles, containing
7 the liquid, active agent formulation, and the polymer
8 ingredients are separately passed through a screen,
9 such as a screen having a mesh of about 40 wires per
10 inch, to reduce any larger sized materials, and dry
11 mixed. Then, a pharmaceutically-acceptable liquid,
12 having a sufficient vapor pressure to allow subsequent
13 drying over a reasonable period of time, for example 24
14 hours, is added to the dry mixture and the damp mass is
15 extruded through a mesh screen (e.g. 20 wires per inch)
16 to further mix the materials. Examples of suitable
17 liquids are water, methanol, ethanol, isopropanol,
18 acetone, and the like. The liquid will need to be
19 compatible with the liquid of the liquid, formulation.

20
21 After the extrusion process, the mixture is allowed to
22 dry, for example in air overnight at room temperature,
23 if the active agent does not require any special
24 handling. After drying, the resulting material is
25 granulated, for example by passing the dried material
26 through a mesh screen (e.g., 20 wires per inch). The
27 granules are combined with a suitable tableting
28 lubricant which has been previously passed through a
29 mesh screen (e.g., 60 wires per inch). The resulting
30 material is tumbled to produce the finished granulation
31 for the tableting process. Tablets are produced using
32 well known methodologies associated with horizontal and

1 vertical compression units using dies and punches of
2 appropriate dimensions. Alternate granulation methods,
3 for example, fluid bed granulation or direct
4 compression granulation can be used as well and such
5 method will be chosen by one skilled in the art
6 depending on the particular nature of the materials
7 being used and the convenience and preference of the
8 fabricator.

9
10 In order to prepare a preferred device of the present
11 invention, the active agent formulation is first
12 prepared and formed into a matrix of the desired size
13 and shape typically by tableting, e.g. by conventional
14 tableting methods. The matrix in its initial prepared
15 form is about the size and dimensions of a size "000"
16 to size 5 hard gelatin capsule. The cross-sectional
17 shape of the matrix may be generally circular or may be
18 oval, triangular, square, hexagonal or other shapes
19 that are easily handled, especially by patients with
20 limited dexterity. Presently preferred shapes are
21 those in which the cross-section is circular or oval.
22 The ring or bands are then placed onto the surface of
23 active agent formulation matrix or printed onto the
24 surface using conventional banding or printing
25 techniques, such as disclosed herein or in U.S. Patent
26 5,534,263, which is incorporated herein by reference.

27
28 The terms "active agent" and "drug" are used
29 interchangeably herein and refer to an agent, active
30 agent, compound, composition of matter or mixture
31 thereof which provides some pharmacologic, often
32 beneficial, effect. This includes foods, food

1 supplements, nutrients, drugs, antiacids, vitamins such
2 as, for example, Vitamin C, Vitamin E, microorganism
3 attenuators and other agents that benefit the
4 environment of use. As used herein, the terms include
5 any physiologically or pharmacologically active
6 substance that produces a localized or systemic effect
7 or effects in animals, including warm blooded mammals,
8 humans and primates; domestic household or farm animals
9 such as cats, dogs, sheep, goats, cattle, horses and
10 pigs; laboratory animals such as mice, rats and guinea
11 pigs; zoo and wild animals; and the like. The active
12 agent that can be delivered includes inorganic and
13 organic compounds, including, without limitation,
14 active agents which act on the peripheral nerves,
15 adrenergic receptors, cholinergic receptors, the
16 skeletal muscles, the cardiovascular system, smooth
17 muscles, the blood circulatory system, synaptic sites,
18 neuroeffector junctional sites, endocrine and hormone
19 systems, the immunological system, the reproductive
20 system, the skeletal system, autacoid systems, the
21 alimentary and excretory systems, the histamine system
22 and the central nervous system.

23
24 Suitable active agents may be selected from, for
25 example, proteins, enzymes, enzyme inhibitors,
26 hormones, polynucleotides, nucleoproteins,
27 polysaccharides, glycoproteins, lipoproteins, peptides,
28 polypeptides, steroids, hypnotics and sedatives,
29 psychic energizers, tranquilizers, anticonvulsants,
30 antidepressants, muscle relaxants, antiparkinson
31 agents, analgesics, immunosuppressants, anti-
32 inflammatories, antihistamines, local anesthetics,

1 muscle contractants, antimicrobials, antimalarials,
2 antivirals, antibiotics, antiobesity agents,
3 antidiabetic agents, hormonal agents including
4 contraceptives, sympathomimetics, polypeptides and
5 proteins capable of eliciting physiological effects,
6 diuretics, lipid regulating agents, antiandrogenic
7 agents, antiparasitics, neoplastics, antineoplastics,
8 antidiabetics, immunosuppressives, antidepressants,
9 antiobesity agents, antihyperglycemics, hypoglycemics,
10 nutritional agents and supplements, growth supplements,
11 fats, ophthalmics, antienteritis agents, electrolytes
12 and diagnostic agents.

13
14 Examples of active agents useful in this form of the
15 invention include prochlorperazine edisylate, ferrous
16 sulfate, albuterol, aminocaproic acid, mecamlamine
17 hydrochloride, procainamide hydrochloride, amphetamine
18 sulfate, methamphetamine hydrochloride, benzphetamine
19 hydrochloride, isoproterenol sulfate, phenmetrazine
20 hydrochloride, bethanechol chloride, methacholine
21 chloride, pilocarpine hydrochloride, atropine sulfate,
22 scopolamine bromide, isopropamide iodide, tridihexethyl
23 chloride, phenformin hydrochloride, metformin,
24 methylphenidate hydrochloride, theophylline cholineate,
25 cephalixin hydrochloride, diphenidol, meclizine
26 hydrochloride, prochlorperazine maleate,
27 phenoxybenzamine, thiethylperazine maleate,
28 anisindione, diphenadione erythrityl tetranitrate,
29 digoxin, isoflurophate, acetazolamide, nifedipine,
30 methazolamide, bendroflumethiazide, chlorpropamide,
31 glipizide, glyburide, gliclazide, tobutamide,
32 chlorproamide, tolazamide, acetohexamide, troglitazone,

1 orlistat, bupropion, nefazodone, tolazamide,
2 chlormadinone acetate, phenaglycodol, allopurinol,
3 aluminum aspirin, methotrexate, acetyl sulfisoxazole,
4 hydrocortisone, hydrocorticosterone acetate, cortisone
5 acetate, dexamethasone and its derivatives such as
6 betamethasone, triamcinolone, methyltestosterone, 17-
7 β -estradiol, ethinyl estradiol, ethinyl estradiol
8 3-methyl ether, prednisolone, 17- β -hydroxyprogesterone
9 acetate, 19-nor-progesterone, norgestrel,
10 norethindrone, norethisterone, norethiederone,
11 progesterone, norgesterone, norethynodrel, terfandine,
12 fexofenadine, aspirin, acetaminophen, indomethacin,
13 naproxen, fenoprofen, sulindac, indoprofen,
14 nitroglycerin, isosorbide dinitrate, propranolol,
15 timolol, atenolol, alprenolol, cimetidine, clonidine,
16 imipramine, levodopa, selegiline, chlorpromazine,
17 methyldopa, dihydroxyphenylalanine, calcium gluconate,
18 ketoprofen, ibuprofen, cephalexin, erythromycin,
19 haloperidol, zomepirac, ferrous lactate, vincamine,
20 phenoxybenzamine, diltiazem, milrinone, captopril,
21 mandol, guanbenz, hydrochlorothiazide, ranitidine,
22 flurbiprofen, fenbufen, fluprofen, tolmetin,
23 alclofenac, mefenamic, flufenamic, difuninal,
24 nimodipine, nitrendipine, nisoldipine, nicardipine,
25 felodipine, lidoflazine, tiapamil, gallopamil,
26 amlodipine, mioflazine, lisinopril, enalapril,
27 captopril, ramipril, enalaprilat, famotidine,
28 nizatidine, sucralfate, etintidine, tetratolol,
29 minoxidil, chlordiazepoxide, diazepam, amitriptyline,
30 and imipramine, and pharmaceutical salts of these
31 active agents. Further examples are proteins and
32 peptides which include, but are not limited to,

1 cyclosporins such as cyclosporine A, insulin,
2 colchicine, glucagon, thyroid stimulating hormone,
3 parathyroid and pituitary hormones, calcitonin, renin,
4 prolactin, corticotrophin, thyrotropic hormone,
5 follicle stimulating hormone, chorionic gonadotropin,
6 gonadotropin releasing hormone, bovine somatotropin,
7 porcine somatotropin, oxytocin, vasopressin, prolactin,
8 somatostatin, lypressin, pancreozymin, luteinizing
9 hormone, LHRH, interferons, interleukins, growth
10 hormones such as human growth hormone, bovine growth
11 hormone and porcine growth hormone, fertility
12 inhibitors such as the prostaglandins, fertility
13 promoters, growth factors, and human pancreas hormone
14 releasing factor.

15
16 In this form, the present invention is particularly
17 useful to deliver active agents that are poorly
18 absorbed in the lower gastrointestinal tract, but well
19 absorbed in the upper gastrointestinal tract (i.e., the
20 small intestine) or active agents that exhibit poor
21 solubility such that the increased retention time in
22 the stomach allows for a greater quantity of active
23 agent to dissolve from the dosage form than would
24 otherwise be dissolved. Typically, antiviral,
25 antifungal and antibiotic agents, e.g. sulfonamides,
26 quinolones, penicillins, cephalosporins,
27 aminoglycosides, and tetracyclines, are representative
28 classes of agents for which the invention is
29 particularly useful. Such antibiotic agents may
30 include, for example, β -lactam antibiotics, vancomycin,
31 clidamycin, erythromycin, trimethoprim-
32 sulfamethoxazole, rifampin, ciprofloxacin,

1 amoxicillin, clindamycin, ceftriaxone, cefotaxime,
2 chloramphenicol, clindamycin, cefoxitin, doxycycline,
3 spectinomycin, ofloxacin, rifampin, minocycline,
4 doxycycline, aztreonam, imipenem, meropenem,
5 nitrofurantoin, azithromycin, atovaquone, trimetrexate,
6 dapsone, primaquin, trimetrexate, ketoconazole,
7 fluconazole, amphotericin B, itraconazole,
8 trifluridine, foscarnet, zidovudine, amantadine,
9 interferon alfa, sulfonamides such as sulfisoxazole,
10 sulfadiazine, and sulfasalazine, quinolones and
11 fluoroquinolones such as, for example, cinoxacin,
12 ofloxacin, diprofloxacin, ofloxacin, sparfloxacin,
13 lomefloxacin, fleroxacin, pefloxacin and amifloxacin,
14 gentamicin, tobramycin, amikacin, netilmicin,
15 kanamycin, and neomycin. Representative antiviral
16 agents include acyclovir, famciclovir, foscarnet,
17 ganciclovir, idoxuridine, sorivudine, trifluridine,
18 valacyclovir, vidarabine, didanosine, stavudine,
19 zalcitabine, zidovudine, amantadine, interferons, e.g.,
20 interferon alpha, ribavirin, rimantadine, nucleoside RT
21 inhibitors, such as lamivudine and adefovir, non-
22 nucleoside inhibitors such as nevirapine, delamanid,
23 zalcitabine, saquinavir and indinavir, nucleoside DNA
24 polymerase inhibitors such as famciclovir, fialuridine, cidofovir
25 and lobucavir, antisense oligonucleotides such as
26 alovirsen, receptor decoys such as sICAM-1, capsid
27 binding agents such as pirodavir, and neuraminidase
28 inhibitors such as GG167.

29

30 The dosage form of the embodiment of the invention is
31 useful for the delivery of oral, hypoglycemic agents,
32 such as the sulfonylureas, e.g., tolbutamide,

1 glyburide, glipizide and gliclazide, the biguamides,
2 e.g., metformin and phenformin, and the
3 thiazolidinediones, e.g. ciglitazone and pioglitazone.
4 Also, immunosuppressives, such as, for example,
5 cyclosporine, tacrolimus (Fk506) and micophenolate
6 mofetil.

7
8 Specific examples of active agents that are readily
9 absorbed in the upper gastrointestinal tract relative
10 to the lower gastrointestinal tract are acyclovir,
11 ganciclovir, cimetidine, ranitidine, captopril,
12 methyldopa, selegiline and the like. Specific examples
13 of active agents that exhibit poor solubility in water
14 are diphenidol, meclizine hydrochloride,
15 prochlorperazine maleate, phenoxybenzamine,
16 triethylperazine maleate, anisindone, diphenadione
17 erythrityl tetranitrate, digoxin, isoflurophate,
18 acetazolamide, methazolamide, bendroflumethiazide,
19 chlorpropamide, tolazamide, chlormadionone acetate,
20 phenaglycodol, allopurinol, aluminum aspirin,
21 methotrexate, acetyl sulfisoxazole, erythromycin,
22 progestins, estrogenic, progestational
23 corticosteroids, hydrocortisone, hydrocorticosterone
24 acetate, cortisone acetate, tramcinolone,
25 methyltestosterone, 17-beta-estradiol, ethinyl estradiol,
26 prazosin hydrochloride, ethinyl estradiol 3-methyl
27 ether, prednisolone, 17-alpha-hydroxyprogesterone
28 acetate, 19-norprogesterone, norgestrel, norethindrone,
29 progesterone, norgesterone, norethlynodrel, and the
30 like.

31

1 Retention of the dosage form of the present invention.
2 in the stomach for a prolonged period of time makes it
3 especially useful for the localized treatment of
4 gastric acidity, gastrointestinal disorders, such as
5 duodenal ulcers, peptic ulcers and chronic gastritis,
6 and the eradication of *Helicobacter pylori*.
7 Representative active agents for such uses include
8 cimetidine, ranitidine, famotidine, nizatidine,
9 zolentine, omeprazole, lansoprazole and active agents
10 useful for the treatment of *Helicobacter pylori*, such
11 as metronidazole, timidazole, amoxicillin,
12 clarithromycin, minocycline and tetracycline.

13
14 While for reasons of efficacy, safety, economy,
15 convenience and/or efficiency it may be desirable to
16 utilize a single active agent in the active agent
17 formulation, it is to be understood that more than one
18 active agent may be incorporated into the active agent
19 formulation in a device of this form of the invention,
20 and that the use of the term "agent" or "active agent"
21 in no way excludes the use of two or more such agents
22 or active agents. The agents can be in various forms,
23 such as uncharged molecules, components of molecular
24 complexes or nonirritating, pharmacologically
25 acceptable salts. Also, simple derivatives of the
26 agents (such as ethers, esters, amides, etc) which are
27 easily hydrolyzed by body pH, enzymes, etc, can be
28 employed. Combinations of two or more active agents
29 can optionally be co-delivered, simultaneously or
30 sequentially from the dosage form of this invention.

31

1 The dosage form of this form of the invention may
2 include additional ingredients, such as, for example, a
3 buffer or other agents for controlling pH in the
4 stomach or elsewhere in the gastrointestinal tract, an
5 agent or agents for delaying onset of the housekeeping
6 wave, preferably locally delivered by the dosage form
7 in amounts not resulting in any substantial systemic
8 effect to the subject, as for example, anticholinergic
9 agents such as propantheline, and other agents
10 including, but not limited to, methylcellulose, guar
11 gum, fats such as triglyceride esters, e.g., triethanol
12 myristate, fatty acids of 10-15 carbon atoms, and the
13 like, a viscosity regulating vehicle, a surfactant, a
14 dye, a permeation enhancer, a proteinase inhibitor, or
15 other formulation ingredients and additives, as are
16 known in the art.

17
18 The present dosage form may also include minor amounts
19 of low molecular weight polymers, which serve useful
20 functions in tablet formation, for example, to improve
21 the tablet cohesiveness after compression or to improve
22 the physical or chemical stability of the dosage form.
23 These polymers are added at quantities less than 10% by
24 weight and preferably less than 5% by weight of the
25 tablet. Examples of such polymers include
26 hydroxypropyl methyl cellulose having molecular weights
27 of less than 20,000 grams per mole, methylcellulose
28 having a molecular weight of less than 20,000 grams per
29 mole, polyvinyl pyrrolidone having a molecular weight
30 of less than 50,000 grams per mole, and the like.
31

1 The amount of active agent employed in the present
2 dosage form will be that amount necessary to deliver a
3 therapeutically effective amount of the agent to
4 achieve the desired therapeutic result. In practice,
5 this will vary widely depending upon the particular
6 agent, the degree of active agent absorption, the
7 severity of the condition, and the desired therapeutic
8 effect. Thus, it is not practical to define a
9 particular range for the therapeutically effective
10 amount of each active agent incorporated into the
11 device. Such ranges can easily be determined by one
12 skilled in the art using conventional methods, for
13 example from dose ranging and plasma level studies.
14 Any references to specific quantities of active agent
15 or specific dose ranges of active agent herein are
16 intended to include the amount or amounts of active
17 agent specified and bioequivalents thereof.

18
19 When the delivery device of this form of the invention
20 is being used to substitute for one or more doses of an
21 active agent presented in a conventional dosage form
22 that is usually prescribed for multiple dosing during a
23 predetermined period, the sum of the amounts of active
24 agent present in the multiple doses of the conventional
25 dosage form for use in the period may be used to
26 determine an upper limit on the of the amount of active
27 agent to be included in the device of this invention.
28 For example, if the conventional dosage form contains
29 200 mg of active agent and is to be administered every
30 3 hours, a dosage form of this invention may be
31 prepared for administration every 6 hours, and that

1 dosage form may contain 400 mg of active agent which
2 will be delivered over the 6 hour period.

3

4 However, when compliance with multiple dosing is a
5 problem, the advantage of administering the dosage
6 forms of the invention at fewer times throughout a
7 twenty-four hour period may provide incentive to
8 incorporate greater amounts of active agent, where such
9 greater amounts do not have any deleterious effects.

10 The specific amount of active agent to be included in
11 the dosage form of the invention can easily be
12 determined by routine dosage studies that compare the
13 blood plasma active agent levels of subjects with
14 conventional dosing and the dosage form of this
15 invention.

16

17 The dosage forms of this form of the invention can
18 conveniently release active agent in a controlled and
19 sustained manner over a prolonged period. Typically,
20 active agent will be released from the dosage form at a
21 rate that releases a therapeutically effective amount
22 of active agent to the subject over a substantial
23 portion of the period between administration of the
24 dosage forms. Typically, release will occur over 40%
25 of the period between repeated administration of the
26 dosage form, more preferably at least over 60% of the
27 period, and most preferably over 80% of the period.

28

29 In an especially preferred embodiment, the invention
30 comprises porous particles in which is sorbed liquid,
31 active agent formulation dispersed in a polymer
32 composition having from about 10 weight percent to

1 about 50 weight percent of a water-soluble, high
2 molecular weight polyethylene oxide polymer and from
3 about 10 weight percent to about 60 weight percent of a
4 water-insoluble hydroxypropyl cellulose polymer. The
5 polyethylene oxide polymer has a molecular weight of
6 between about 100,000 and 10,000,000 grams per mole.
7 The hydroxypropyl cellulose polymer preferably has a
8 hydroxypropyl content of between about 8-15 weight
9 percent, and most preferably between about 10-13 weight
10 percent.

11

12 The following examples are illustrative of the gastric
13 retentive embodiment of the present invention.

14

15

16

PREPARATION 1

17

18 A general procedure for preparing the dosage forms of
19 the present invention is described below with the
20 exemplary active agent being cyclosporin. Various
21 other materials or additives as described herein may be
22 used in place of or in addition to the specific
23 materials provided in this description in the same or
24 other proportions based on the desired final
25 characteristics of the dosage forms to be fabricated.

26

27 A self-emulsifying drug solution comprising, in weight
28 percent, 2% cyclosporin, 49% polyoxyl 35 castor oil
29 (Cremophor EL, BASF Corporation) and 49% distilled
30 acetylated monoglyceride (Myvacet 9-45) is prepared.
31 Then, 15 g of the solution is blended with 35 g of
32 porous calcium hydrogen phosphate (FujiCalin) in a
33 mixing vessel. 3.6 Grams of the gel-forming polymer
polyethylene oxide, having a number average molecular

1 weight of approximately 7 million grams per mole, is
2 separately screened through a mesh having 40 wires per
3 inch. The polyethylene oxide is supplied under the
4 trade name Polyox[®] grade 303 as manufactured by Union
5 Carbide Corporation, Danbury, Connecticut. The sized
6 active agent and polymer are mixed. Then, 8.25 grams
7 of a hydroattractant water-insoluble polymer,
8 hydroxypropyl cellulose having a hydroxypropyl content
9 of 10-13 weight percent and an average fiber particle
10 size of 50 microns, is sieved through the 40-mesh
11 screen and blended into the mixture. The hydroxypropyl
12 cellulose is supplied as Low-Substituted Hydroxypropyl
13 Cellulose grade 11 as manufactured by Shin-Etsu
14 Chemical Company, Ltd., Tokyo, Japan. Anhydrous ethyl
15 alcohol, specially denatured formula 3A, i.e., ethanol
16 denatured with 5 volume percent methanol, is added to
17 the mixture with stirring until a uniformly damp mass
18 formed. The damp mass is extruded through a screen
19 having 20 wires per inch. The extrudate is then
20 allowed to air dry at room temperature overnight.
21 After drying, the resulting extrudate is passed again
22 through a 20-mesh sieve, forming granules. 0.15 Grams
23 of the tableting lubricant, magnesium stearate, is
24 passed through a sieve having 60 wires per inch. The
25 sized 60-mesh lubricant is then tumbled into the
26 granules to produce the finished granulation.
27
28 Portions of the resulting granulation are weighed and
29 compacted with caplet-shaped tooling on a Carver press
30 at pressure head of 1.5 tons. Each tablet will contain
31 a target weight of active agent and be of a suitable
32 size to be orally administered. The shape of the

1 tablet may have approximately cylindrical proportions,
2 and the diameter may be approximately 7.5 millimeters
3 (mm) and the length approximately 22 mm.

4
5 A tube of polyolefin material having an outside
6 diameter of about 0.1 mm larger than the diameter of
7 the tablet and having a wall thickness of 0.25 mm is
8 sliced with a razor to produce rings. The width of
9 each ring is approximately 3 mm. One ring is then
10 press fitted onto each caplet such that the ring, or
11 band, is located approximately at the midpoint of the
12 length of the caplet. This step completes the
13 fabrication procedure for the dosage form.

14 15 ASSAY

16 The dosage forms fabricated in Preparation 1 may be
17 placed in a beaker of simulated gastric fluid, as
18 specified in U.S. Pharmacopedia/National Formulary
19 23/18, having a pH of approximately 1.2 and a
20 maintained temperature of 37° C to determine release of
21 active agent over time. Additionally, the swollen size
22 of the dosage form may be removed and measured for
23 dimensional change. A swollen device has the general
24 appearance of the dosage form shown in Figure 3.

25 26 EXAMPLE 6

27 Equivalent amounts of the following polymers may be
28 substituted for the polyethylene oxide in Preparation 1
29 (all molecular weights are number average molecular
30 weights in grams per mole): hydroxypropyl cellulose
31 (MW: 1,000,000), hydroxypropyl methyl cellulose (MW:
32 254,000), hydroxyethyl cellulose (MW: 1,300,000),

1 sodium carboxy methylcellulose (MW: 700,000), calcium
2 carboxymethyl cellulose (MW: 700,000), methyl cellulose
3 (MW: 135,000), and polyvinyl alcohol (Elvanol® HV), and
4 dosage forms with a polyethylene band are fabricated to
5 the same dimensions as described in Preparation 1 with
6 equivalent quantities of the active agents acyclovir,
7 ganciclovir, minocycline metformin and cyclosporin.
8 The prepared dosage forms are retained in the stomach
9 of a dog for a prolonged retention period and deliver
10 the active agents over a prolonged period of time.

11

12

13

EXAMPLE 7

14 Dosage forms containing equivalent quantities of the
15 active agents of EXAMPLE 7 are prepared according to
16 the procedures in Preparation 1, except that the
17 nonwater soluble hydroattractant used is, respectively,
18 microcrystalline cellulose (Avicel), cross-linked
19 sodium or calcium carboxymethyl cellulose, cellulose
20 fiber (Solka-Floc, Elcema, Arbocel), cross-linked
21 polyvinyl pyrrolidone (Polyplasdone XL), cross-linked
22 Amberlite resin, alginates (Satialgine), colloidal
23 magnesium-aluminum silicate (Veegum), corn starch
24 granules, rice starch granules, potato starch granules,
25 and sodium carboxymethyl starch (Expotab, Primojel).
26 The prepared dosage forms are retained in the stomach
27 of a subject and deliver active agent over a prolonged
28 period of time.

29

30

EXAMPLE 8

31 The following active agents are substituted, in the
32 quantities indicated in the parentheses following each

1 active agent listed, for the quantity of active agent
2 in Example 6: cimetidine (400 mg; 800 mg, 1200 mg, 1600
3 mg), ranitidine (150 mg; 200 mg, 300 mg), captopril
4 (12.5 mg; 25 mg; 50 mg; 100 mg, 150 mg), methyldopa
5 (125; 250; 500 mg), and selegiline (5 mg, 10 mg) and
6 the dosage forms are prepared in the same manner as
7 described in Example 6. The prepared dosage forms are
8 retained in the stomach of a subject and deliver active
9 agent over a prolonged period of time.

10

11

12

13

EXAMPLE 9

14 Dosage forms of this invention containing metformin are
15 fabricated according to the procedures of Preparation
16 1, except that the tablet is inserted into a size "00"
17 hard gelatin capsule before banding. The band is
18 applied by a printing process using the methods and
19 compositions described in U.S. Patent 5,534,263,
20 incorporated herein by reference, where the band
21 material is ethyl acrylate/methyl methacrylate 70:30
22 copolymer (Eudragit NE 30 D, Rohm Tech). The resulting
23 dosage form is smooth and easy to swallow.

24

25

26

EXAMPLE 10

27 A gastric platform dosage form for an insoluble drug,
28 metformin free base, is prepared in accordance with the
29 procedures of Preparation 1 by substituting a
30 drug/particle/Polyox mass consisting of 2% metformin
31 base, 38% corn oil, 40% Neusilin and 20% Polyox 303 for
32 the sized active agent-polymer mixture. Then the
33 hydroattractant is added to the mixture and the

1 subsequent steps repeated for this formulation, forming
2 a tableted core.

3
4 A solution for use in film coating the tablets is
5 prepared by stirring 40 grams of methyl cellulose
6 (Methocel A15 LV Premium supplied by Dow Chemical,
7 Midland Michigan) and 10 grams of sorbitol 950 grams of
8 purified water at room temperature. The mixture is
9 then chilled overnight at 9° centigrade to complete
10 dissolution. The tablets from above are transferred
11 to a pharmaceutical coating pan spray coated with the
12 solution in a current of warmed air until a dry film
13 coating is deposited onto each tablet.

14
15 An aqueous dispersion for use in banding the tablets is
16 prepared by dissolving 30 grams of triacetin in 174.75
17 grams of ethyl acrylate methylmethacrylate 70:30
18 copolymer aqueous dispersion (Eudragit® NE40D supplied
19 by Rohm Corporation, Darmstadt, West Germany). Then,
20 0.1 grams of anti-foam agent (Simethicone Q7-2587, Dow
21 Chemical, Midland, Michigan) is blended into the
22 mixture. This formed the final composition of the
23 banding dispersion.

24
25 The film coated tablets from above are then banded by
26 applying a the above banding dispersion in a transfer
27 printing process using a printing wheel having a width
28 of approximately 100 mils (2.54 mm). The banded system
29 is then dried in warm air to remove the water from the
30 aqueous dispersion, leaving a single band located in
31 the center of the caplet having a width of
32 approximately 120 mils (3.05 mm) and a weight of

1 approximately 21 mg. The entire banded system is then
2 overcoated with more of the aqueous-based film coat
3 solution using the formulation and process as described
4 above until a film coat weight of approximately 30 mg
5 is applied. The dosage forms so prepared are retained
6 in the stomach of a dog and deliver active agent over a
7 prolonged period of time.

8
9 In relation to the third embodiment of the present
10 invention exemplified by Figures 6 and 7, they are best
11 understood by reference to the following definitions,
12 the drawings and exemplary disclosure provided herein.

13

14 Definitions

15 By "active agent", "drug", or "compound", which are
16 used interchangeably herein, is meant an agent , drug,
17 compound, composition of matter or mixture thereof
18 which provides some physiological, psychological,
19 biological, or pharmacological, and often beneficial,
20 effect when in the environment of use.

21

22 By "uniform rate of release" or "uniform release rate"
23 is meant a rate of release of the active agent from a
24 dosage form that does not vary positively or negatively
25 by more than 30% from the mean rate of release of the
26 active agent over a prolonged period of time, as
27 determined in a USP Type 7 Interval Release Apparatus.
28 Preferred uniform rates of release will vary by not
29 more than 25% (positively or negatively) from the mean
30 rate of release determined over a prolonged period of
31 time.

32

1 By "prolonged period of time" or "prolonged period" is
2 meant a continuous period of time of 4 hours or more,
3 more typically 6 hours or more.

4
5 By "dosage form" is meant a pharmaceutical composition
6 or device comprising an active pharmaceutical agent,
7 the composition or device optionally containing
8 inactive ingredients, such as pharmaceutically-
9 acceptable carriers, excipients, suspension agents,
10 surfactants, disintegrants, binders, diluents,
11 lubricants, stabilizers, antioxidants, osmotic agents,
12 colorants, plasticizers, and the like, that are used to
13 manufacture and deliver active pharmaceutical agents.

14
15 By "pharmaceutically-acceptable acid addition salt" or
16 "pharmaceutically-acceptable salt", which are used
17 interchangeably herein, are meant those salts in which
18 the anion does not contribute significantly to the
19 toxicity or pharmacological activity of the salt, and,
20 as such, they are the pharmacological equivalents of
21 the bases of the compounds to which they refer.

22 Examples of pharmaceutically acceptable acids that are
23 useful for the purposes of salt formation include but
24 are not limited to hydrochloric, hydrobromic,
25 hydroiodic, citric, acetic, benzoic, mandelic,
26 phosphoric, nitric, mucic, isethionic, palmitic, and
27 others.

28
29 By "sustained release " is meant continuous release of
30 active agent to an environment of use over a prolonged
31 period.

32

1 By "pulsatile release" is meant release of an active
2 agent to an environment of use for one or more discrete
3 periods of time preceded or followed by (i) at least
4 one discrete period of time in which the active agent
5 is not released, or (ii) at least one period of time in
6 which another, different active agent is released.
7 Pulsatile release is meant to include delayed release
8 of active agent following administration of the dosage
9 form and release in which one or more pulses of active
10 agent are released over a period of time.

11

12 By "steady state" is meant the condition in which the
13 amount of drug present in the blood plasma of a subject
14 does not vary significantly over a prolonged period of
15 time.

16

17 By "release rate assay" is meant a standardized assay
18 for the determination of a compound using a USP Type 7
19 interval release apparatus substantially in accordance
20 with the description of the assay contained herein. It
21 is understood that reagents of equivalent grade may be
22 substituted in the assay in accordance with generally-
23 accepted procedures. Also, different fluids such as
24 artificial gastric fluid or artificial intestinal fluid
25 may be used to evaluate release characteristics in
26 environments characterized by different pH values.

27

28 By "liquid, active agent formulation" is meant that the
29 active agent is present in a composition that is
30 miscible with or dispersible in the fluids of the
31 environment of use, or is able to flow or diffuse from
32 the pores of the particles into the environment of use.

1 The formulation may be neat, liquid active agent, or a
2 solution, suspension, slurry, emulsion, self-
3 emulsifying composition, colloidal dispersion or other
4 flowable composition in which the active agent is
5 present.

6
7 The active agent may be accompanied by a suspension
8 agent, antioxidant, emulsion former, protecting agent,
9 permeation enhancer and the like. The amount of an
10 active agent in a dosage form generally is about 0.05
11 ng to 5 g or more, with individual dosage forms
12 comprising, for example, 25 ng, 1 mg, 5 mg, 10 mg, 25
13 mg, 100 mg, 250 mg, 500 mg, 750 mg, 1.0 g, 1.2 g, and
14 the like, of active agent. The system typically can be
15 administered once, twice or thrice daily for
16 pharmaceutical applications, or more or less as
17 required by the particular application. In
18 agricultural applications, systems typically will be
19 applied at longer intervals, such as weekly, monthly,
20 seasonally or the like.

21
22 One of the most suitable devices for the controlled
23 release of liquid active agent formulations in
24 accordance with this form of the invention is that
25 having a semipermeable wall defining a compartment, an
26 expandable push layer and a drug layer in the
27 compartment, and an exit orifice formed in the dosage
28 form to permit the drug layer to be dispensed. Within
29 the drug layer is a carrier in which is dispersed a
30 plurality of porous particles in which the liquid,
31 active agent has been sorbed. As the push layer
32 expands, the carrier comprising the drug layer will be

1 forced from the dosage form substantially in the dry
2 state where it will erode and release the porous
3 particles containing the liquid, active agent
4 formulation. After release, the liquid active agent
5 formulation will be immediately available the
6 environment of use in the liquid state, and the porous
7 particles will themselves disintegrate or erode and
8 further release the active agent formulation.

9
10 When manufacturing such dosage forms, a common practice
11 is to fabricate a compressed tablet comprising the drug
12 layer and the push layer. Typically, the drug layer
13 composition, conveniently in granulated or powdered
14 form, is compressed in a die cavity of a vertical
15 tableting press. Then the push layer composition,
16 also conveniently in granular or powdered form, is
17 placed in the die cavity above the drug layer and
18 compressed as well to form a bilayer tablet. During
19 the compression or compacting step of the drug layer,
20 the porous particles should be sufficiently resistant
21 to the compressive forces so as not to be crushed or
22 pulverized to any significant extent and prematurely
23 release the liquid, active agent formulation from the
24 porous particles.

25
26 Materials useful for sorbing the liquid active agent
27 formulations have already been described herein. Other
28 absorptive materials may be substituted for the
29 foregoing. For example, powders of microcrystalline
30 cellulose sold under the tradenames Avicel (FMC
31 Corporation) and Elcema (Degussa) and porous

1 agglomerated silicon dioxide, sold under the tradenames
2 Cab-O-Sol (Cabot) and Aerosil (Degussa), may be used.

3
4 The liquid, active agent formulation may be in any form
5 that can be dispensed from the inside of the pores as
6 the drug layer disintegrates in the environment of use.
7 The formulation, for example, may be neat, liquid
8 active agent, liquid active agent in a solution,
9 suspension, emulsion or self-emulsifying composition,
10 or the like, or a liposomal solution or solid
11 formulation, or solid active agent in solution,
12 suspension or slurry. Optionally other dosage-forming
13 ingredients, such as an anti-oxidant, a suspending
14 agent, a surface active agent, and the like may be
15 present in the liquid, active agent formulation. The
16 liquid, active agent formulation will be released in a
17 form most suitable to provide active agent to the site
18 of delivery in a state in which it may be rapidly
19 absorbed in the environment of use to provide its
20 beneficial action with minimum delay once delivered to
21 the absorption site.

22
23 It often is desirable to provide the dosage form with a
24 flow-promoting layer or lubricant that facilitates
25 complete release of the drug layer from the compartment
26 formed by the semipermeable wall since the formed
27 bilayer tablet may be formed with surface
28 irregularities that impede the release of the drug
29 layer from the dosage form and sometimes results in
30 incomplete release of the drug layer.

31

1 Dosage forms of this form of the invention release
2 effective amounts of active agent to the patient over a
3 prolonged period of time and often provide the
4 opportunity for less frequent dosing, including once-a-
5 day dosing, than previously required for immediate
6 release compositions. The dosage forms of this
7 invention comprise a composition containing a liquid,
8 active agent formulation contained in porous particles
9 dispersed in a bioerodible carrier.

10

11 Active agents include, *inter alia*, foods, food
12 supplements, nutrients, drugs, antiacids, vitamins,
13 microorganism attenuators and other agents that provide
14 a benefit in the environment of use and may be
15 dissolved, suspended or otherwise dispersed in a liquid
16 to form a liquid, active agent formulation. Active
17 agents include any physiologically or pharmacologically
18 active substance that produces a localized or systemic
19 effect or effects in animals, including warm blooded
20 mammals, humans and primates; domestic household or
21 farm animals such as cats, dogs, sheep, goats, cattle,
22 horses and pigs; laboratory animals such as mice, rats
23 and guinea pigs; zoo and wild animals; and the like.
24 Active agents that can be delivered include inorganic
25 and organic compounds as previously discussed which act
26 on the peripheral nerves, etc.

27

28 Suitable active agents and examples of particular
29 useful active agents are as previously discussed for
30 the second embodiment exemplified hereinbefore.

31

1 The method of this invention may be applied generally
2 to liquid formulations such as contained in
3 commercially-available dosage forms as previously
4 described and exemplified herein.

5
6 The dosage form may also contain a chelating agent as
7 previously discussed, either combined with the liquid,
8 active agent formulation in the porous particles, or
9 incorporated into the drug layer in which the porous
10 particles are dispersed.

11
12 A dosage form 20 intended for continuous, zero order
13 release of the active agent is illustrated in Figure 6.
14 As can be seen therein, the dosage form 20 comprises a
15 wall 22 defining a cavity 24. Wall 22 is provided with
16 an exit orifice 26. Within cavity 24 and remote from
17 the exit orifice 26 is a push layer 28. A drug layer
18 30 is located within cavity 24 adjacent exit orifice
19 26. A plurality of porous particles 10 is dispersed in
20 carrier 18 within the cavity 24 to form the drug layer
21 30. An optional, flow-promoting layer 32, the function
22 of which will be described and which may be formed as a
23 secondary wall, extends between drug layer 30 and the
24 inner surface of wall 22. An orifice 26 is provided at
25 one end of dosage form 20 to permit expression of the
26 drug layer 30 from the dosage form upon expansion of
27 push layer 28.

28
29 The wall 22 is formed to be permeable to the passage of
30 an external fluid, such as water and biological fluids,
31 and it is substantially impermeable to the passage of
32 active agent, osmagent, osmopolymer and the like. As

1 such, it is semipermeable. The selectively
2 semipermeable compositions used for forming the wall
3 are essentially nonerodible and they are insoluble in
4 biological fluids during the life of the dosage form.
5 Wall 22 need not be semipermeable in its entirety, but
6 at least a portion of wall 22 should be semipermeable
7 to allow fluid to contact or communicate with push
8 layer 28 such that push layer 28 imbibes fluid during
9 use. Specific materials for the fabrication of
10 semipermeable wall 22 are well known in the art, and
11 representative examples of such materials are described
12 later herein.

13
14 Secondary wall 32, which functions as the flow-
15 promoting layer or lubricant, is in contacting position
16 with the inner surface of the semipermeable wall 22 and
17 at least the external surface of the drug layer that is
18 opposite wall 22; although the secondary wall 32 may,
19 and preferably will, extend to, surround and contact
20 the external surface of the push layer. Wall 32
21 typically will surround at least that portion of the
22 external surface of the drug layer that is opposite the
23 internal surface of wall 22. Secondary wall 32 may be
24 formed as a coating applied over the compressed core
25 comprising the drug layer and the push layer. The
26 outer semipermeable wall 22 surrounds and encases the
27 inner, secondary wall 32. Secondary wall 32 is
28 preferably formed as a subcoat of at least the surface
29 of the drug layer 30, and optionally the entire
30 external surface of the compacted drug layer 30 and the
31 push layer 28. When the semipermeable wall 22 is
32 formed as a coat of the composite formed from the drug

1 layer 30, the push layer 28 and the secondary wall 32,
2 contact of the semipermeable wall 22 with the inner
3 coat is assured.

4

5 Figure 7 illustrates another form of the invention
6 wherein the dosage form 20 includes a placebo layer 38
7 which serves to delay release of particles 10 the
8 environment of use. The other components of the dosage
9 form 20 are substantially the same as those described
10 with reference to Figure 6, and like components are
11 designated with the same reference numerals. The
12 extent of the delay that may be afforded by the placebo
13 layer will in part depend on the volume of the placebo
14 layer 38 which has to be displaced by the push layer 28
15 as it imbibes fluid and expands. Figures 9-13
16 illustrate different periods of delay that may be
17 obtained by varying the placebo layer 38 when
18 delivering a representative compound progesterone. The
19 dosage forms for which the results in Figures 9-13 are
20 illustrated correspond to those described in Examples
21 12-16, respectively. Delays of 2 hours to 10 hours are
22 illustrated.

23

24 Representative polymers for forming wall 22 comprise
25 semipermeable homopolymers, semipermeable copolymers,
26 and the like. Such materials comprise cellulose
27 esters, cellulose ethers and cellulose ester-ethers.
28 The cellulosic polymers have a degree of substitution
29 (DS) of their anhydroglucose unit of from greater than
30 0 up to 3, inclusive. Degree of substitution (DS) means
31 the average number of hydroxyl groups originally
32 present on the anhydroglucose unit that are replaced by

1 a substituting group or converted into another group.
2 The anhydroglucose unit can be partially or completely
3 substituted with groups such as acyl, alkanoyl,
4 alkenoyl, aroyl, alkyl, alkoxy, halogen, carboalkyl,
5 alkylcarbamate, alkylcarbonate, alkylsulfonate,
6 alkylsulfamate, semipermeable polymer forming groups,
7 and the like, wherein the organic moieties contain from
8 one to twelve carbon atoms, and preferably from one to
9 eight carbon atoms.

10

11 The semipermeable compositions typically include a
12 member selected from the group consisting of cellulose
13 acylate, cellulose diacylate, cellulose triacylate,
14 cellulose acetate, cellulose diacetate, cellulose
15 triacetate, mono-, di- and tri-cellulose alkanylates,
16 mono-, di-, and tri-alkenylates, mono-, di-, and tri-
17 aroylates, and the like. Exemplary polymers include
18 cellulose acetate having a DS of 1.8 to 2.3 and an
19 acetyl content of 32 to 39.9%; cellulose diacetate
20 having a DS of 1 to 2 and an acetyl content of 21 to
21 35%; cellulose triacetate having a DS of 2 to 3 and an
22 acetyl content of 34 to 44.8%; and the like. More
23 specific cellulosic polymers include cellulose
24 propionate having a DS of 1.8 and a propionyl content
25 of 38.5%; cellulose acetate propionate having an acetyl
26 content of 1.5 to 7% and an acetyl content of 39 to
27 42%; cellulose acetate propionate having an acetyl
28 content of 2.5 to 3%, an average propionyl content of
29 39.2 to 45%, and a hydroxyl content of 2.8 to 5.4%;
30 cellulose acetate butyrate having a DS of 1.8, an
31 acetyl content of 13 to 15%, and a butyryl content of
32 34 to 39%; cellulose acetate butyrate having an acetyl

1 content of 2 to 29%, a butyryl content of 17 to 53%,
2 and a hydroxyl content of 0.5 to 4.7%; cellulose
3 triacylates having a DS of 2.6 to 3, such as cellulose
4 trivalerate, cellulose trilaminate, cellulose
5 tripalmitate, cellulose trioctanoate and cellulose
6 tripropionate; cellulose diesters having a DS of 2.2 to
7 2.6, such as cellulose disuccinate, cellulose
8 dipalmitate, cellulose dioctanoate, cellulose
9 dicaprylate, and the like; and mixed cellulose esters,
10 such as cellulose acetate valerate, cellulose acetate
11 succinate, cellulose propionate succinate, cellulose
12 acetate octanoate, cellulose valerate palmitate,
13 cellulose acetate heptanoate, and the like.
14 Semipermeable polymers are known in U.S. Patent No.
15 4,077,407, and they can be synthesized by procedures
16 described in Encyclopedia of Polymer Science and
17 Technology, Vol. 3, pp. 325-354 (1964), Interscience
18 Publishers Inc., New York, NY.
19
20 Additional semipermeable polymers for forming the outer
21 wall 22 comprise cellulose acetaldehyde dimethyl
22 acetate; cellulose acetate ethylcarbamate; cellulose
23 acetate methyl carbamate; cellulose
24 dimethylaminoacetate; semipermeable polyamide;
25 semipermeable polyurethanes; semipermeable sulfonated
26 polystyrenes; cross-linked selectively semipermeable
27 polymers formed by the coprecipitation of an anion and
28 a cation, as disclosed in U.S. Patents Nos. 3,173,876;
29 3,276,586; 3,541,005; 3,541,006 and 3,546,142;
30 semipermeable polymers, as disclosed by Loeb, et al. in
31 U.S. Patent No. 3,133,132; semipermeable polystyrene
32 derivatives; semipermeable poly(sodium

1 styrenesulfonate); semipermeable
2 poly(vinylbenzyltrimethylammonium chloride); and
3 semipermeable polymers exhibiting a fluid permeability
4 of 10^{-5} to 10^{-2} (cc. mil/cm hr.atm), expressed as per
5 atmosphere of hydrostatic or osmotic pressure
6 differences across a semipermeable wall. The polymers
7 are known to the art in U.S. Patents Nos. 3,845,770;
8 3,916,899 and 4,160,020; and in Handbook of Common
9 Polymers, Scott and Roff (1971) CRC Press, Cleveland,
10 OH.
11
12 Wall 22 also can comprise a flux regulating agent. The
13 flux regulating agent is a compound added to assist in
14 regulating the fluid permeability or flux through wall
15 22. The flux regulating agent can be a flux enhancing
16 agent or a decreasing agent. The agent can be
17 preselected to increase or decrease the liquid flux.
18 Agents that produce a marked increase in permeability
19 to fluid such as water, are often essentially
20 hydrophilic, while those that produce a marked decrease
21 to fluids such as water, are essentially hydrophobic.
22 The amount of regulator in the wall when incorporated
23 therein generally is from about 0.01% to 20% by weight
24 or more. The flux regulator agents in one embodiment
25 that increase flux include polyhydric alcohols,
26 polyalkylene glycols, polyalkylenediols, polyesters of
27 alkylene glycols, and the like. Typical flux enhancers
28 include polyethylene glycol 300, 400, 600, 1500, 4000,
29 6000 and the like; low molecular weight glycols such as
30 polypropylene glycol, polybutylene glycol and
31 polyamylene glycol: the polyalkylenediols such as
32 poly(1,3-propanediol), poly(1,4-butanediol), poly(1,6-

1 hexanediol), and the like; aliphatic diols such as 1,3-
2 butylene glycol, 1,4-pentamethylene glycol, 1,4-
3 hexamethylene glycol, and the like; alkylene triols
4 such as glycerine, 1,2,3-butanetriol, 1,2,4-
5 hexanetriol, 1,3,6-hexanetriol and the like; esters
6 such as ethylene glycol dipropionate, ethylene glycol
7 butyrate, butylene glucol dipropionate, glycerol
8 acetate esters, and the like. Representative flux
9 decreasing agents include phthalates substituted with
10 an alkyl or alkoxy or with both an alkyl and alkoxy
11 group such as diethyl phthalate, dimethoxyethyl
12 phthalate, dimethyl phthalate, and [di(2-ethylhexyl)
13 phthalate], aryl phthalates such as triphenyl
14 phthalate, and butyl benzyl phthalate; insoluble salts
15 such as calcium sulphate, barium sulphate, calcium
16 phosphate, and the like; insoluble oxides such as
17 titanium oxide; polymers in powder, granule and like
18 form such as polystyrene, polymethylmethacrylate,
19 polycarbonate, and polysulfone; esters such as citric
20 acid esters esterfied with long chain alkyl groups;
21 inert and substantially water impermeable fillers;
22 resins compatible with cellulose based wall forming
23 materials, and the like.

24
25 Other materials that can be used to form the wall 22
26 for imparting flexibility and elongation properties to
27 the wall, for making wall 22 less-to-nonbrittle and to
28 render tear strength, include phthalate plasticizers
29 such as dibenzyl phthalate, dihexyl phthalate, butyl
30 octyl phthalate, straight chain phthalates of six to
31 eleven carbons, di-isononyl phthalte, di-isodecyl
32 phthalate, and the like. The plasticizers include

1 nonphthalates such as triacetin, dioctyl azelate,
2 epoxidized tallate, tri-isooctyl trimellitate, tri-
3 isononyl trimellitate, sucrose acetate isobutyrate,
4 epoxidized soybean oil, and the like. The amount of
5 plasticizer in a wall when incorporated therein is
6 about 0.01% to 20% weight, or higher.

7
8 The drug layer 30 comprises a composition formed of a
9 liquid active agent formulation absorbed in porous
10 particles, the preferred characteristics of the
11 particles being described elsewhere herein, and a
12 carrier, such as a hydrophilic polymer. The
13 hydrophilic polymer provides a hydrophilic polymer
14 composition in the drug layer that may contribute to
15 the uniform release rate of active agent and controlled
16 delivery pattern by controlling the rate of release of
17 the porous particles containing the liquid, active
18 agent formulation from the dosage form. Representative
19 examples of these polymers are poly(alkylene oxide) of
20 100,000 to 750,000 number-average molecular weight,
21 including poly(ethylene oxide), poly(methylene oxide),
22 poly(butylene oxide) and poly(hexylene oxide); and a
23 poly(carboxymethylcellulose) of 40,000 to 400,000
24 number-average molecular weight, represented by
25 poly(alkali carboxymethylcellulose), poly(sodium
26 carboxymethylcellulose), poly(potassium
27 carboxymethylcellulose) and poly(lithium
28 carboxymethylcellulose). The drug composition can
29 comprise a hydroxypropylalkylcellulose of 9,200 to
30 125,000 number-average molecular weight for enhancing
31 the delivery properties of the dosage form as
32 represented by hydroxypropylethylcellulose,

1 hydroxypropyl methylcellulose,
2 hydroxypropylbutylcellulose and
3 hydroxypropylpentylcellulose; and a
4 poly(vinylpyrrolidone) of 7,000 to 75,000 number-
5 average molecular weight for enhancing the flow
6 properties of the dosage form. Preferred among those
7 polymers are the poly(ethylene oxide) of 100,000 -
8 300,000 number average molecular weight. Carriers that
9 erode in the gastric environment, i.e., bioerodible
10 carriers, are especially preferred.

11
12 Surfactants and disintegrants may be utilized in the
13 carrier as well. Exemplary of the surfactants are
14 those having an HLB value of between about 10 - 25,
15 such as polyethylene glycol 400 monostearate,
16 polyoxyethylene-4-sorbitan monolaurate,
17 polyoxyethylene-20-sorbitan monooleate,
18 polyoxyethylene-20-sorbitan monopalmitate,
19 polyoxyethylene-20-monolaurate, polyoxyethylene-40 -
20 stearate, sodium oleate and the like. Disintegrants
21 may be selected from starches, clays, celluloses,
22 algin and gums and crosslinked starches, celluloses
23 and polymers. Representative disintegrants include corn
24 starch, potato starch, croscarmellose, crospovidone,
25 sodium starch glycolate, Veegum HV, methylcellulose,
26 agar, bentonite, carboxymethylcellulose, alginic acid,
27 guar gum and the like.

28
29 The drug layer 30 is formed as a mixture containing the
30 porous particles and the carrier. The carrier portion
31 of the drug layer may be formed from particles by
32 comminution that produces the desired size of the

1 carrier particle used in the fabrication of the drug
2 layer. The means for producing carrier particles
3 include granulation, spray drying, sieving,
4 lyophilization, crushing, grinding, jet milling,
5 micronizing and chopping to produce the intended micron
6 particle size. The process can be performed by size
7 reduction equipment, such as a micropulverizer mill, a
8 fluid energy grinding mill, a grinding mill, a roller
9 mill, a hammer mill, an attrition mill, a chaser mill,
10 a ball mill, a vibrating ball mill, an impact
11 pulverizer mill, a centrifugal pulverizer, a coarse
12 crusher and a fine crusher. The size of the particle
13 can be ascertained by screening, including a grizzly
14 screen, a flat screen, a vibrating screen, a revolving
15 screen, a shaking screen, an oscillating screen and a
16 reciprocating screen. The processes and equipment for
17 preparing drug and carrier particles are disclosed in
18 Pharmaceutical Sciences, Remington, 17th Ed., pp. 1585-
19 1594 (1985); Chemical Engineers Handbook, Perry, 6th
20 Ed., pp. 21-13 to 21-19 (1984); Journal of
21 Pharmaceutical Sciences, Parrot, Vol. 61, No. 6, pp.
22 813-829 (1974); and Chemical Engineer, Hixon, pp. 94-
23 103 (1990).

24
25 The active compound may be provided in the liquid
26 active agent formulation in amounts of from 1 microgram
27 to 5000 mg per dosage form, depending upon the required
28 dosing level that must be maintained over the delivery
29 period, i.e., the time between consecutive
30 administrations of the dosage forms. More typically,
31 loading of compound in the dosage forms will provide
32 doses of compound to the subject ranging from 1

1 microgram to 2500 mg per day, more usually 1 mg to 2500
2 mg per day. The drug layer typically will be a
3 substantially dry composition formed by compression of
4 the carrier and the porous particles, with the
5 understanding that the porous particles will have
6 contained therein the liquid, active agent formulation.
7 The push layer will push the drug layer from the exit
8 orifice as the push layer imbibes fluid from the
9 environment of use, and the exposed drug layer will be
10 eroded to release the porous particles into the
11 environment of use. This may be seen with reference to
12 Figure 6.

13
14 The push layer 28 is an expandable layer having a push-
15 displacement composition in direct or indirect
16 contacting layered arrangement with the drug layer 30.
17 When in indirect contacting layered arrangement, an
18 inert element (not shown), such as a spacer layer or
19 disk, may be placed between the drug layer and the push
20 layer. If several pulses of active agent are to be
21 delivered from a single dosage form, similar inert
22 layers may be interposed between discrete portions of
23 drug layer. The inert layer(s) may be sized to provide
24 appropriate time delay(s) between pulses of active
25 agent and the volume of each discrete drug layer will
26 provide control of the time period over which the pulse
27 of active agent is delivered. Inert layers may be
28 formed of materials utilized to form the push layer 28,
29 or if desired, formed of materials that are easily
30 compacted but do not swell in the fluid environment of
31 use.
32

1 Push layer 28 comprises a polymer that imbibes an
2 aqueous or biological fluid and swells to push the drug
3 composition through the exit means of the device.
4 Representatives of fluid-imbibing displacement polymers
5 comprise members selected from poly(alkylene oxide) of
6 1 million to 15 million number-average molecular
7 weight, as represented by poly(ethylene oxide) and
8 poly(alkali carboxymethylcellulose) of 500,000 to
9 3,500,000 number-average molecular weight, wherein the
10 alkali is sodium, potassium or lithium. Examples of
11 additional polymers for the formulation of the push-
12 displacement composition comprise osmopolymers
13 comprising polymers that form hydrogels, such as
14 Carbopol[®] acidic carboxypolymer, a polymer of acrylic
15 cross-linked with a polyallyl sucrose, also known as
16 carboxypolymethylene, and carboxyvinyl polymer having a
17 molecular weight of 250,000 to 4,000,000; Cyanamer[®]
18 polyacrylamides; cross-linked water swellable
19 indenemaleic anhydride polymers; Good-rite[®] polyacrylic
20 acid having a molecular weight of 80,000 to 200,000;
21 Aqua-Keeps[®] acrylate polymer polysaccharides composed of
22 condensed glucose units, such as diester cross-linked
23 polygluran; and the like. Representative polymers that
24 form hydrogels are known to the prior art in U.S.
25 Patent No. 3,865,108, issued to Hartop; U.S. Patent No.
26 4,002,173, issued to Manning; U.S. Patent No.
27 4,207,893, issued to Michaels; and in Handbook of
28 Common Polymers, Scott and Roff, Chemical Rubber Co.,
29 Cleveland, OH.

30
31 The osmagent, also known as osmotic solute and
32 osmotically effective agent, which exhibits an osmotic

1 pressure gradient across the outer wall and subcoat,
2 comprises a member selected from the group consisting
3 of sodium chloride, potassium chloride, lithium
4 chloride, magnesium sulfate, magnesium chloride,
5 potassium sulfate, sodium sulfate, lithium sulfate,
6 potassium acid phosphate, mannitol, urea, inositol,
7 magnesium succinate, tartaric acid raffinose, sucrose,
8 glucose, lactose, sorbitol, inorganic salts, organic
9 salts and carbohydrates.

10
11 Use of the inner wall or subcoat 32 is optional, but
12 presently preferred. The inner subcoat 32 typically
13 may be 0.01 to 5 mm thick, more typically 0.025-0.25 mm
14 thick, although a thicker subcoat, for example 0.5 to
15 5mm thick, may be used in certain applications. The
16 inner subcoat 32 comprises a member selected from
17 hydrogels, gelatin, low molecular weight polyethylene
18 oxides, e.g., less than 100,000 MW,
19 hydroxyalkylcelluloses, e.g., hydroxyethylcellulose,
20 hydroxypropylcellulose, hydroxyisopropylcellulose,
21 hydroxybutylcellulose and hydroxyphenylcellulose, and
22 hydroxyalkyl alkylcelluloses, e.g., hydroxypropyl
23 methylcellulose, and mixtures thereof. The
24 hydroxyalkylcelluloses comprises polymers having a
25 9,500 to 1,250,000 number-average molecular weight.
26 For example, hydroxypropyl celluloses having number
27 average molecular weights of between 80,000 to 850,000
28 are useful. The flow promoting layer may be prepared
29 from conventional solutions or suspensions of the
30 aforementioned materials in aqueous solvents or inert
31 organic solvents. Preferred materials for the subcoat
32 or flow promoting layer include hydroxypropyl

1 cellulose, hydroxyethyl cellulose, hydroxypropyl methyl
2 cellulose, povidone [poly(vinylpyrrolidone)],
3 polyethylene glycol, and mixtures thereof. More
4 preferred are mixtures of hydroxypropyl cellulose and
5 povidone, prepared in organic solvents, particularly
6 organic polar solvents such as lower alkanols having 1-
7 8 carbon atoms, preferably ethanol, mixtures of
8 hydroxyethyl cellulose and hydroxypropyl methyl
9 cellulose prepared in aqueous solution, and mixtures of
10 hydroxyethyl cellulose and polyethylene glycol prepared
11 in aqueous solution. Most preferably, the subcoat
12 consists of a mixture of hydroxypropyl cellulose and
13 povidone prepared in ethanol. Conveniently, the weight
14 of the subcoat applied to the bilayer core may be
15 correlated with the thickness of the subcoat and
16 residual drug remaining in a dosage form in a release
17 rate assay such as described herein. During
18 manufacturing operations, the thickness of the subcoat
19 may be controlled by controlling the weight of the
20 subcoat taken up in the coating operation. When wall
21 32 is fabricated of a gel-forming material, contact
22 with water in the environment of use facilitates
23 formation of a gel or gel-like inner coat having a
24 viscosity that may promote and enhance slippage between
25 outer wall 22 and drug layer 30.

26
27 Exemplary solvents suitable for manufacturing the
28 respective walls, layers, coatings and subcoatings
29 utilized in the dosage forms of the invention comprise
30 aqueous and inert organic solvents that do not
31 adversely harm the materials utilized to fabricate the
32 dosage forms. The solvents broadly include members

1 selected from the group consisting of aqueous solvents,
2 alcohols, ketones, esters, ethers, aliphatic
3 hydrocarbons, halogenated solvents, cycloaliphatics,
4 aromatics, heterocyclic solvents and mixtures thereof.
5 Typical solvents include acetone, diacetone alcohol,
6 methanol, ethanol, isopropyl alcohol, butyl alcohol,
7 methyl acetate, ethyl acetate, isopropyl acetate, n-
8 butyl acetate, methyl isobutyl ketone, methyl propyl
9 ketone, n-hexane, n-heptane, ethylene glycol monoethyl
10 ether, ethylene glycol monoethyl acetate, methylene
11 dichloride, ethylene dichloride, propylene dichloride,
12 carbon tetrachloride nitroethane, nitropropane
13 tetrachloroethane, ethyl ether, isopropyl ether,
14 cyclohexane, cyclooctane, benzene, toluene, naphtha,
15 1,4-dioxane, tetrahydrofuran, diglyme, water, aqueous
16 solvents containing inorganic salts such as sodium
17 chloride, calcium chloride, and the like, and mixtures
18 thereof such as acetone and water, acetone and
19 methanol, acetone and ethyl alcohol, methylene
20 dichloride and methanol, and ethylene dichloride and
21 methanol.

22
23 Pan coating may be conveniently used to provide the
24 completed dosage form, except for the exit orifice. In
25 the pan coating system, the subcoat on the wall-forming
26 compositions is deposited by successive spraying of the
27 respective composition on the bilayered core comprising
28 the drug layer and the push layer accompanied by
29 tumbling in a rotating pan. A pan coater is used
30 because of its availability at commercial scale. Other
31 techniques can be used for coating the drug core.
32 Finally, the wall or coated dosage form are dried in a

1 forced-air oven, or in a temperature and humidity
2 controlled oven to free the dosage form of solvent.
3 Drying conditions will be conventionally chosen on the
4 basis of available equipment, ambient conditions,
5 solvents, coatings, coating thickness, and the like.

6
7 Other coating techniques can also be employed. For
8 example, the semipermeable wall and the subcoat of the
9 dosage form can be formed in one technique using the
10 air-suspension procedure. This procedure consists of
11 suspending and tumbling the bilayer core in a current
12 of air, an inner subcoat composition and an outer
13 semipermeable wall forming composition, until, in
14 either operation, the subcoat and the outer wall coat
15 is applied to the bilayer core. The air-suspension
16 procedure is well suited for independently forming the
17 wall of the dosage form. The air-suspension procedure
18 is described in U.S. Patent No. 2,799,241; in J. Am.
19 Pharm. Assoc., Vol. 48, pp. 451-459 (1959); and, ibid.,
20 Vol. 49, pp. 82-84 (1960). The dosage form also can be
21 coated with a Wurster[®] air-suspension coater using, for
22 example, methylene dichloride methanol as a cosolvent.
23 An Aeromatic[®] air-suspension coater can be used
24 employing a cosolvent.

25
26 The dosage form of the invention may be manufactured by
27 standard techniques. For example, the dosage form may
28 be manufactured by the wet granulation technique. In
29 the wet granulation technique a solution, suspension or
30 dispersion of the active agent in a liquid is mixed
31 with the porous particles to allow the liquid, active
32 agent formulation to sorb into the pores of the porous

1 particles. Then the carrier is blended with the porous
2 particles using an organic solvent, such as denatured
3 anhydrous ethanol, as the granulation fluid. After a
4 wet blend is produced, the wet mass blend is forced
5 through a predetermined screen onto trays. The blend
6 is dried under ambient conditions until the desired
7 moisture level is obtained. The drying conditions are
8 not so severe, however, that the liquid of the liquid,
9 active agent formulation is allowed to evaporate to any
10 significant extent. Next, a lubricant such as
11 magnesium stearate or agglomerated silicon dioxide
12 (Cab-O-Sil) for example, is added to the blend, which
13 is then put into milling jars and mixed on a jar mill
14 for several minutes. The composition is pressed into a
15 layer, for example, in a Manesty[®] press. The first
16 compressed layer is typically the drug layer, and then
17 the push layer may be pressed against the composition
18 forming the drug layer, and the bilayer tablets are fed
19 to the Kilian[®] Dry Coater and surrounded with the drug-
20 free coat, followed by the exterior wall solvent
21 coating. In those instances where a trilayer dosage
22 form for pulsatile release having a placebo layer is to
23 be fabricated, the placebo layer is usually formed
24 first, then the drug layer is pressed onto the placebo
25 layer to form a bilayer composition, and then the push
26 layer is compressed onto the bilayer core to form the
27 trilayer composition. The trilayer tablet is then
28 provided with the optional subcoat and the membrane
29 coat for the rate controlling membrane. It is
30 apparent, however, that the order in which the
31 respective layers are compressed may be different, but
32 the foregoing is preferred.

1
2 In another manufacture the porous particles containing
3 the liquid, active agent formulation and other
4 ingredients comprising the drug layer are blended and
5 pressed into a solid layer. The layer possesses
6 dimensions that correspond to the internal dimensions
7 of the area the layer is to occupy in the dosage form,
8 and it also possesses dimensions corresponding to the
9 second layer for forming a contacting arrangement
10 therewith. The drug layer components can also be
11 blended with a solvent and mixed into a solid or
12 semisolid form by conventional methods, such as
13 ballmilling, calendering, stirring or rollmilling, and
14 then pressed into a preselected shape. Next, the
15 expandable layer, e.g., a layer of osmopolymer
16 composition, is placed in contact with the layer of
17 drug in a like manner. The layering of the drug
18 formulation and the osmopolymer layer can be fabricated
19 by conventional two-layer press techniques. The two
20 contacted layers are first coated with the flow-
21 promoting subcoat and then an outer semipermeable wall.
22 The air-suspension and air-tumbling procedures comprise
23 in suspending and tumbling the pressed, contacting
24 first and second layers in a current of air containing
25 the delayed-forming composition until the first and
26 second layers are surrounded by the wall composition.
27
28 The dosage form of the invention is provided with at
29 least one exit orifice. The exit orifice cooperates
30 with the drug core for the uniform release of drug from
31 the dosage form. The exit orifice can be provided
32 during the manufacture of the dosage form or during

1 drug delivery by the dosage form in a fluid environment
2 of use. The expression "exit orifice" as used for the
3 purpose of this invention includes a member selected
4 from the group consisting of a passageway; an aperture;
5 an orifice; and a bore. The expression also includes
6 an orifice that is formed from a substance or polymer
7 that erodes, dissolves or is leached from the outer
8 coat or wall or inner coat to form an exit orifice.
9 The substance or polymer may include an erodible
10 poly(glycolic) acid or poly(lactic) acid in the outer
11 or inner coats; a gelatinous filament; a water-
12 removable poly(vinyl alcohol); a leachable compound,
13 such as a fluid removable pore-former selected from the
14 group consisting of inorganic and organic salt, oxide
15 and carbohydrate. An exit, or a plurality of exits,
16 can be formed by leaching a member selected from the
17 group consisting of sorbitol, lactose, fructose,
18 glucose, mannose, galactose, talose, sodium chloride,
19 potassium chloride, sodium citrate and mannitol to
20 provide a uniform-release dimensioned pore-exit
21 orifice. The exit orifice can have any shape, such as
22 round, triangular, square, elliptical and the like for
23 the uniform metered dose release of a drug from the
24 dosage form. The dosage form can be constructed with
25 one or more exits in spaced apart relation or one or
26 more surfaces of the dosage form. The exit orifice can
27 be performed by drilling, including mechanical and
28 laser drilling, through the outer coat, the inner coat,
29 or both. Exits and equipment for forming exits are
30 disclosed in U.S. Patents Nos. 3,845,770 and 3,916,899,
31 by Theeuwes and Higuchi; in U.S. Patent No. 4,063,064,
32 by Saunders, et al.; and in U.S. Patent No. 4,088,864,

1 by Theeuwes, et al. The exit orifice may be from 10%
2 to 100% of the inner diameter of the compartment formed
3 by wall 22, preferably from 30% to 100%, and most
4 preferably from 50% to 100%.

5
6 The continuous release dosage forms provide a uniform
7 rate of release of compound over a prolonged period of
8 time, typically from about zero hours, the time of
9 administration, to about 4 hours to 20 hours or more,
10 often for 4 hours to 16 hours, and more usually for a
11 time period of 4 hours to 10 hours. At the end of a
12 prolonged period of uniform release, the rate of
13 release of drug from the dosage form may decline
14 somewhat over a period of time, such as several hours.
15 The dosage forms provide therapeutically effective
16 amounts of drug for a broad range of applications and
17 individual subject needs. The results of the release
18 of progesterone from a representative, continuous
19 release dosage form of this invention is provided in
20 Figure 8. As can be seen therefrom, progesterone is
21 released over a period of time extending up to about 15
22 hours. In Figure 8, the filled circles represent a
23 drug granulation that does not contain any PVP
24 (polyvinylpyrrolidone), the empty triangles represent a
25 drug granulation containing 10% PVP, and the filled
26 squares and filled triangles represent drug
27 granulations containing 10% maltose. In each case, the
28 dosage forms were formed as trilayer, continuous system
29 with (1) a mannitol layer adjacent the exit orifice
30 that quickly dissolves in the release bath, (2) a drug
31 layer containing progesterone dispersed in Cremophor
32 EL/Myvacet in calcium hydrogen phosphate in a ratio of

1 45/55 % by weight as described in greater detail in
2 Example 11, and (3) a push layer.

3

4 The dosage forms may also provide active agent in a
5 pulsatile release profile. With reference to Figures
6 9-13, varying delays in the onset of the release of
7 active agent are illustrated. Those results are
8 achieved with the dosage forms described in Examples
9 12-16, respectively. By varying the volume of the
10 placebo layer, it was possible to control the initial
11 period before active agent is released from the dosage
12 form.

13

14 With zero order release, upon initial administration,
15 the dosage forms may provide a drug concentration in
16 the plasma of the subject that increases over an
17 initial period of time, typically several hours or
18 less, and then provide a relatively constant
19 concentration of drug in the plasma over a prolonged
20 period of time, typically 4 hours to 24 hours or more.
21 The release profiles of the dosage forms of this
22 invention provide release of drug over the entire 24-
23 hour period corresponding to once-a-day administration,
24 such that steady state concentration of drug in blood
25 plasma of a subject may be maintained at
26 therapeutically effective levels over a 24 hour period
27 after administration the sustained release dosage form.
28 Steady state plasma levels of drug may typically be
29 achieved after twenty-four hours or, in some cases,
30 several days, e.g., 2-5 days, in most subjects.

31

1 Dosage forms of this invention release drug at a
2 uniform rate of release over a prolonged period of time
3 as determined in a standard release rate assay such as
4 that described herein. When administered to a subject,
5 the dosage forms of the invention provide blood plasma
6 levels of drug in the subject that are less variable
7 over a prolonged period of time than those obtained
8 with immediate release dosage forms. When the dosage
9 forms of this invention are administered on a regular,
10 once-a-day basis, the dosage forms of the invention
11 provide steady state plasma levels of drug such that
12 the difference between C_{\max} and C_{\min} over the 24-hour
13 period is substantially reduced over that obtained from
14 administration of an immediate release product that is
15 intended to release the same amount of drug in the 24-
16 hour period as is provided from the dosage forms of the
17 invention

18

19 The dosage forms of this invention may be adapted to
20 release active agent at a uniform rate of release rate
21 over a prolonged period of time, preferably 4-6 hours
22 or more. Measurements of release rate are typically
23 made *in vitro*, in acidified water, simulated gastric
24 fluid or simulated intestinal fluid to provide a
25 simulation of conditions in specific biological
26 locations, and are made over finite, incremental time
27 periods to provide an approximation of instantaneous
28 release rate. Information of such *in vitro* release
29 rates with respect to a particular dosage form may be
30 used to assist in selection of dosage form that will
31 provide desired *in vivo* results. Such results may be
32 determined by present methods, such as blood plasma

1 assays and clinical observation, utilized by
2 practitioners for prescribing available immediate
3 release dosage forms.

4
5 Dosage forms of the present invention having zero order
6 release rate profiles as described herein may provide
7 to a patient a substantially constant blood plasma
8 concentration and a sustained therapeutic effect of
9 active agent, after administration of the dosage form,
10 over a prolonged period of time. The sustained release
11 dosage forms of this invention demonstrate less
12 variability in drug plasma concentration over a 24-hour
13 period than do immediate release formulations, which
14 characteristically create significant peaks in drug
15 concentration shortly or soon after administration to
16 the subject.

17
18 The dosage forms of the invention may have a delayed
19 onset of action incorporated directly into the dosage
20 form by means of the placebo layer that has been
21 described. For particular applications, it may be
22 desirable to deliver a plurality of the dosage forms,
23 with or without a placebo layer or other drug layer
24 design, at a single location in the gastrointestinal
25 tract. This may effected conveniently by combining the
26 dosage forms of the invention with associated
27 technology, such as for example, the Chronset[®] drug
28 delivery system of Alza Corporation, Palo Alto,
29 California. Such systems can be programmed to release
30 the dosage forms at designated times and at targeted
31 absorption sites. That technology is described in US
32 Patents Nos. 5,110,597; 5,223,265; 5,312,390; 5,443,459;

1 5,417,682; 5,498,255; 5,531,736; and 5,800,422, which
2 are incorporated herein by reference. The composite
3 delivery system may be manufactured by loading the
4 osmotic dosage forms described herein into the
5 Chronset® systems, and provide for the controlled
6 release of active agent in a variety of formats.

7
8 An illustrative general method of manufacturing dosage
9 forms of this form of the invention is described below
10 in PREPARATION 2. Percentages are percentages by
11 weight unless noted otherwise. Variations in the
12 methods and substitution of materials may be made and
13 will be apparent from the earlier description.
14 Equivalent or proportional amounts of such materials
15 may be substituted for those used in the PREPARATION 2.
16 More specific descriptions are provided in the Examples
17 and alternative materials and procedures are
18 illustrated therein.

19

20 PREPARATION 2

21

22 Preparation of the Drug Layer.
23 A binder solution is prepared by adding hydroxypropyl
24 cellulose (Klucel MF, Aqualon Company), "HPC", to water
25 to form a solution containing 5 mg of HPC per 0.995
26 grams of water. The solution is mixed until the
27 hydroxypropyl cellulose is dissolved. For a particular
28 batch size, a fluid bed granulator ("FBG") bowl is
29 charged with the required amounts of liquid, active
30 agent formulation and the corresponding amount of porous
31 particles, such as exemplified by the calcium hydrogen
32 phosphate particles sold under the trademark FujiCalin.

1 After the liquid is absorbed by the particles, the blend
2 is mixed with, polyethylene oxide (MW 200,000) (Polyox®
3 N-80, Union Carbide Corporation) (20.3%), hydroxypropyl
4 cellulose (Klucel MF) (5%), polyoxyl 40 stearate (3%)
5 and crospovidone (2%). After mixing the semi-dry
6 materials in the bowl, the binder solution prepared as
7 above is added. Then the granulation is dried in the
8 FBG to a dough-like consistency suitable for milling,
9 and the granulation is milled through a 7 or a 10 mesh
10 screen.

11
12 The granulation is transferred to a tote blender or a V-
13 blender. The required amounts of antioxidant, butylated
14 hydroxytoluene ("BHT") (0.01%), and lubricant, stearic
15 acid (1%), are sized through a 40 mesh screen and both
16 are blended into the granulation using the tote or V-
17 blender until uniformly dispersed (about 1 minute of
18 blending for stearic acid and about 10 minutes of
19 blending for BHT.

20
21 Preparation of the Osmotic Push Layer Granulation.
22 A binder solution is prepared by adding hydroxypropyl
23 methylcellulose 2910 ("HPMC") to water in a ratio of 5
24 mg of HPMC to 1 g of water. The solution is mixed until
25 the HPMC is dissolved. Sodium chloride powder (30%) and
26 red ferric oxide (1.0%) are milled and screened. A
27 fluid bed granulator ("FBG") bowl is charged with the
28 required amounts of polyethylene oxide (MW 7,000,000)
29 (Polyox® 303) (63.7%), HPMC (5.0%), the sodium chloride
30 and the red ferric oxide. After mixing the dry materials
31 in the bowl, the binder solution prepared above is
32 added. The granulation is dried in the FBG until the

1 target moisture content (< 1% by weight water) is
2 reached. The granulation is milled through a 7 mesh
3 screen and transferred to a tote blender or a V-blender.
4 The required amount of antioxidant, butylated
5 hydroxytoluene, (0.08%), is sized through a 60 mesh
6 screen. The required amount of lubricant, stearic acid
7 (0.25%), is sized through a 40 mesh screen and both
8 materials are blended into the granulation using the
9 tote or V-blender until uniformly dispersed (about 1
10 minute for stearic acid and about 10 minutes for BHT).

11

12 Bilayer Core Compression.

13 A longitudinal tablet press (Korsch press) is set up
14 with round, deep concave punches and dies. Two feed
15 hoppers are placed on the press. The drug layer prepared
16 as above is placed in one of the hoppers while the
17 osmotic push layer prepared as above is placed in the
18 remaining hopper.

19

20 The initial adjustment of the tableting parameters (drug
21 layer) is performed to produce cores with a uniform
22 target drug layer weight. The second layer adjustment
23 (osmotic push layer) of the tableting parameters is
24 performed which bonds the drug layer to the osmotic
25 layer to produce cores with a uniform final core weight,
26 thickness, hardness, and friability. The foregoing
27 parameters can be adjusted by varying the fill space
28 and/or the force setting. A typical tablet containing a
29 target amount of drug may be approximately 0.465 inches
30 long and approximately 0.188 inches in diameter.

31

1 Preparation of the Subcoat Solution and Subcoated
2 System.

3 The subcoat solution is prepared in a covered stainless
4 steel vessel. The appropriate amounts of povidone (K29-
5 32) (2.4%) and hydroxypropyl cellulose (MW 80,000)
6 (Klucel EF, Aqualon Company) (5.6%) are mixed into
7 anhydrous ethyl alcohol (92%) until the resulting
8 solution is clear. The bilayer cores prepared above are
9 placed into a rotating, perforated pan coating unit.
10 The coater is started and after the coating temperature
11 of 28 -36 °C is attained, the subcoating solution
12 prepared above is uniformly applied to the rotating
13 tablet bed. When a sufficient amount of solution has
14 been applied to provide the desired subcoat weight gain,
15 the subcoat process is stopped. The desired subcoat
16 weight will be selected to provide acceptable residuals
17 of drug remaining in the dosage form as determined in
18 the release rate assay for a 24-hour period. Generally,
19 it is desirable to have less than 10%, more preferably
20 less than 5%, and most preferably less than 3% of
21 residual drug remaining after 24 hours of testing in a
22 standard release rate assay as described herein, based
23 on the initial drug loading. This may be determined
24 from the correlation between subcoat weight and the
25 residual drug for a number of dosage forms having the
26 same bilayer core but different subcoat weights in the
27 standard release rate assay.

28

29 Preparation of the Rate Controlling Membrane and
30 Membrane Coated System.

31 Subcoated bilayer cores prepared as above are placed
32 into a rotating, perforated pan coating unit. The

1 coater is started, and after the coating temperature (28
2 - 38 °C) is attained, a coating solution such as
3 illustrated in A, B or C below is uniformly applied to
4 the rotating tablet bed until the desired membrane
5 weight gain is obtained. At regular intervals
6 throughout the coating process, the weight gain is
7 determined and sample membrane coated units may be
8 tested in the release rate assay to determine a T_{90} for
9 the coated units. Weight gain may be correlated with T_{90}
10 for membranes of varying thickness in the release rate
11 assay. When sufficient amount of solution has been
12 applied, conveniently determined by attainment of the
13 desired membrane weight gain for a desired T_{90} , the
14 membrane coating process is stopped.

15 Illustrative rate controlling membrane compositions:

16 A. A coating solution is prepared in a covered
17 stainless steel vessel. The appropriate amounts of
18 acetone (565 mg) and water (29.7 mg) are mixed with the
19 poloxamer 188 (1.6 mg) and cellulose acetate (29.7 mg)
20 until the solids are completely dissolved. The coating
21 solution has about 5% solids upon application.

22 B. Acetone (505.4 mg) is mixed with cellulose acetate
23 (27.72 mg) until the cellulose acetate is completely
24 dissolved. Polyethylene glycol 3350 (0.28 mg) and water
25 (26.6 mg) are mixed in separate container. The two
26 solutions are mixed together until the resulting
27 solution is clear. The coating solution has about 5%
28 solids upon application.

29 C. Acetone (776.2 mg) is mixed with cellulose acetate
30 (42.57 mg) until the cellulose acetate is completely
31 dissolved. Polyethylene glycol 3350 (0.43 mg) and water
32 (40.9 mg) are mixed in separate container. The two

1 solutions are mixed together until the resulting
2 solution is clear. The coating solution has about 5%
3 solids upon application.

4

5 Drilling of Membrane Coated Systems.

6 One exit port is drilled into the drug layer end of the
7 membrane coated system. During the drilling process,
8 samples are checked at regular intervals for orifice
9 size, location, and number of exit ports.

10

11 Drying of Drilled Coated Systems.

12 Drilled coated systems prepared as above are placed on
13 perforated oven trays which are placed on a rack in a
14 relative humidity oven (43-45 % relative humidity) and
15 dried to remove the remaining solvents from the coating
16 layers.

17

18 Color and Clear Overcoats.

19 Optional color or clear coats solutions are prepared in
20 a covered stainless steel vessel. For the color coat 88
21 parts of purified water is mixed with 12 parts of Opadry
22 II [color not critical] until the solution is
23 homogeneous. For the clear coat 90 parts of purified
24 water is mixed with 10 parts of Opadry Clear until the
25 solution is homogeneous. The dried cores prepared as
26 above are placed into a rotating, perforated pan coating
27 unit. The coater is started and after the coating
28 temperature is attained (35-45 °C), the color coat
29 solution is uniformly applied to the rotating tablet
30 bed. When sufficient amount of solution has been
31 applied, as conveniently determined when the desired
32 color overcoat weight gain has been achieved, the color

1 coat process is stopped. Next, the clear coat solution
2 is uniformly applied to the rotating tablet bed. When
3 sufficient amount of solution has been applied, or the
4 desired clear coat weight gain has been achieved, the
5 clear coat process is stopped. A flow agent (e.g., Car-
6 nu-bo wax) is applied to the tablet bed after clear coat
7 application.

8
9 Variations in the foregoing procedure will be apparent
10 to one skilled in the art. The examples are provided to
11 illustrate representative dosage forms of the invention
12 prepared by analogous methods.

13 14 ASSAY

15
16 The release rate of drug from devices containing the
17 dosage forms of the invention may be determined in
18 standardized assays such as the following. The method
19 involves releasing systems into a release liquid
20 medium, such as acidified water (pH 3), artificial
21 gastric fluid or artificial intestinal fluid. Aliquots
22 of sample release rate solutions are injected onto a
23 chromatographic system to quantify the amount of drug
24 released during specified test intervals. Drug is
25 resolved on a C_{18} column and detected by UV absorption
26 at the appropriate wavelength for the drug in question.
27 Quantitation is performed by linear regression analysis
28 of peak areas from a standard curve containing at least
29 five standard points.

30
31 Samples are prepared with the use of a USP Type 7
32 Interval Release Apparatus. Each system (invention

1 device) to be tested is weighed. Then, each system is
2 glued to a plastic rod having a sharpened end, and each
3 rod is attached to a release rate dipper arm. Each
4 release rate dipper arm is affixed to an up/down
5 reciprocating shaker (USP Type 7 Interval Release
6 Apparatus), operating at an amplitude of about 3 cm and
7 2 to 4 seconds per cycle. The rod ends with the
8 attached systems are continually immersed in 50 ml
9 calibrated test tubes containing 50 ml of the release
10 medium, equilibrated in a constant temperature water
11 bath controlled at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. At the end of each
12 time interval specified, typically one hour or two
13 hours, the systems are transferred to the next row of
14 test tubes containing fresh release medium. The
15 process is repeated for the desired number of intervals
16 until release is complete. Then the solution tubes
17 containing released drug are removed and allowed to
18 cool to room temperature. After cooling, each tube is
19 filled to the 50 ml mark, each of the solutions is
20 mixed thoroughly, and then transferred to sample vials
21 for analysis by high pressure liquid chromatography
22 ("HPLC"). Standard solutions of drug are prepared in
23 concentration increments encompassing the range of 5
24 micrograms to about 400 micrograms and analyzed by
25 HPLC. A standard concentration curve is constructed
26 using linear regression analysis. Samples of drug
27 obtained from the release test are analyzed by HPLC and
28 concentration of drug is determined by linear
29 regression analysis. The amount of drug released in
30 each release interval is calculated.

31

32

EXAMPLE 11

1 A delivery system (Fig. 6) is manufactured for
2 dispensing a beneficial drug progesterone in a
3 controlled manner over a prolonged period of time. A
4 self-emulsifying drug solution comprising, in weight
5 percent, 2% progesterone, 49% polyoxyl 35 castor oil
6 (Cremophor EL, BASF Corporation) and 49% distilled
7 acetylated monoglyceride (Myvacet 9-45) is prepared.
8 Then, 38 % of the solution is blended with 47% of porous
9 calcium hydrogen phosphate (FujiCalin SG) in a mixing
10 vessel. Four percent of hydroxypropyl methylcellulose
11 (HPMC E5) dissolved in ethanol is slowly added into the
12 mixing vessel containing the blend, and is mixed with
13 the blend until even consistency of wet mass is
14 attained. The wet mass is passed through a screen and
15 then dried at ambient conditions until the granulation
16 reaches the specified moisture level. The mass is
17 rescreened, and then 10 % of maltose and 1 % magnesium
18 stearate is added to the granules and blended.

19
20 Next, an osmotic-layer forming composition comprising,
21 in weight percent, 58.75% sodium carboxymethyl cellulose
22 (7H4F), 30.0% sodium chloride, 5.0% hydroxypropyl
23 methylcellulose (E5), 1.0% red ferric oxide is prepared
24 by passing each component a 40-mesh stainless steel
25 screen and then blending in a Galtt fluid-bed granulator
26 and sprayed with 5.0% hydroxypropyl cellulose (EF)
27 solution in purified water until homogeneous granules
28 form. These granules are passed through an 8-mesh
29 stainless steel screen and mixed with 0.25% magnesium
30 stearate.

31

1 376 Mg of the drug-layer granules and 169 mg of the
2 osmotic(push)-layer granules are compressed into bi-
3 layer longitudinal caplets using 0.265" round punch and
4 Carver press. The tablets are coated with a subcoat
5 composition comprising 5% of Klucel JF and 95% of
6 ethanol using a Freud Hi-coater. The weight of the
7 subcoat is about 3 mg. Then, the subcoated tablets are
8 coated with a rate-controlling membrane composition.
9 The membrane-forming composition comprises, in weight
10 percent, 85% cellulose acetate having an acetyl content
11 of 39.8% and 15% Pluronic F68. The membrane-forming
12 composition is dissolved in acetone to make a 5% solid
13 solution. The membrane-forming composition is sprayed
14 onto the tablets in a Freud Hi-coater. The membrane
15 weight is about 22 mg. Finally, an exit orifice (230
16 mil) is cut mechanically on the drug-layer side of the
17 system. The final system delivers progesterone in-vitro
18 with a zero order delivery as shown in Figure 5.

19

20

EXAMPLE 12

21 A delivery system (Fig. 7) is manufactured for
22 dispensing a beneficial drug such as progesterone as a
23 delayed pulse. First, a self-emulsifying drug solution
24 comprising, in weight percent, 2% progesterone, 49%
25 Cremophor EL and 49% Myvacet 9-45 is prepared. Then, 38
26 % of the solution is blended with 47% of porous calcium
27 hydrogen phosphate (FujiCalin SG) in a mixing vessel.
28 Four percent of HPMC E5 dissolved in ethanol is slowly
29 added into the mixing vessel containing the blend, and
30 is mixed with the blend until even consistency of wet
31 mass is attained. The wet mass is passed through a
32 screen and then dried at ambient conditions until the

1 granulation reaches the specified moisture level. The
2 mass is rescreened, and then 10 % of maltose and 1 %
3 magnesium stearate is added to the granules and blended.
4
5 Next, an osmotic (push)-layer forming composition
6 comprising, in weight percent, 58.75% sodium
7 carboxymethyl cellulose (7H4F), 30.0% sodium chloride,
8 5.0% hydroxypropyl methylcellulose (E5), 1.0% red ferric
9 oxide is prepared by passing each component a 40-mesh
10 stainless steel screen and then blending in a Galtt
11 fluid-bed granulator and sprayed with 5.0% hydroxypropyl
12 cellulose (EF) solution in purified water until
13 homogeneous granules form. These granules are passed
14 through an 8-mesh stainless steel screen and mixed with
15 0.25% magnesium stearate.
16
17 Then, 50 mg of placebo-layer granules (having the same
18 composition as the osmotic-layer), 195 mg of the drug-
19 layer granules and 165 mg of the osmotic-layer granules
20 are compressed into tri-layer longitudinal caplets using
21 0.265" round punch and Carver press. The tablets are
22 coated with a subcoat composition comprising 5% of
23 Klucel JF and 95% of ethanol using a Freud Hi-coater .
24 The weight of the subcoat is about 3 mg. Then, the
25 subcoated tablets are coated with a rate-controlling
26 membrane composition. The membrane-forming composition
27 comprises, in weight percent, 85% cellulose acetate
28 having an acetyl content of 39.8% and 15% Pluronic F68.
29 The membrane-forming composition is dissolved in acetone
30 to make a 5% solid solution. The membrane-forming
31 composition is sprayed onto the tablets in a Freud Hi-
32 coater. The membrane weight is about 22 mg. Finally,

1 an exit orifice (230 mil) is cut mechanically on the 1st
2 placebo-layer side of the system. The final system
3 delivers progesterone in-vitro with a 2 hour delayed
4 pulse as shown in Figure 9.

5

6

EXAMPLE 13

7 The procedure of Example 12 is repeated in this example
8 for providing the following dosage form:

9

10 A dosage form composed of the drug-layer, osmotic-layer
11 and the membrane, the compositions of which are all
12 identical to those in Example 12 is prepared, except
13 that the placebo-layer weight is 100 mg. The final
14 dosage form delivers progesterone in-vitro with a 3 hour
15 delayed pulse as shown in Figure 10.

16

17

EXAMPLE 14

18 The procedure of Example 12 is repeated in this example
19 for providing the following dosage form:

20

21 A dosage form composed of the drug-layer, osmotic-layer
22 and the membrane, the compositions of which are all
23 identical to those in Example 12 is prepared, except
24 that the placebo-layer weight is 155 mg. The final
25 dosage form delivers progesterone in-vitro with a 5 hour
26 delayed pulse as shown in Figure 11.

27

28

EXAMPLE 15

29 The procedure of Example 12 is repeated in this example
30 for providing the following dosage form:

31

1 A dosage form composed of the drug-layer, osmotic-layer
2 and the membrane, the compositions of which are all
3 identical to those in Example 12 is prepared, except
4 that the placebo-layer weight is 250 mg. The final
5 dosage form delivers progesterone in-vitro with a 6-7
6 hour delayed pulse as shown in Figure 12.

7

8

EXAMPLE 16

9 The procedure of Example 12 is repeated in this example
10 for providing the following dosage form:
11 A dosage form composed of the osmotic-layer and the
12 membrane layer compositions which are identical to those
13 in Example 12 is prepared, except that the placebo-layer
14 weight is 155 mg, the drug-layer granulation is composed
15 of 36% of the drug solution described in Example 12, 44%
16 calcium phosphate, 4% HPMC E5, 1% Mg stearate and 15%
17 maltose, and the weight of the rate-controlling membrane
18 is 105 mg. The final dosage form delivers progesterone
19 in-vitro with a 10-h delayed pulse as shown in
20 Figure 13.

21

22

EXAMPLE 17

23 The following formulations are prepared for the
24 incorporation into the dosage forms illustrated in
25 Figure 6 and Figure 7 in accordance with the general
26 procedures described. All percentages are by weight
27 unless otherwise noted. The Polyox 303 push layer is
28 used as the barrier or delay layer (sometimes denoted as
29 a placebo layer) for those dosage forms illustrated in
30 Figure 7 and as the expandable or push layer in both
31 dosage forms illustrated in Figures 6 and 7. Tableting
32 is done on a Carver press at one-quarter ton pressure.

1

2 Polyox 303 push and delay layer formulation

3 Polyox 303 63.68%

4 Sodium Chloride 30%

5 HPMC E5 5%

6 Red Ferric Oxide 1%

7 Mg Stearate 0.25%

8 BHT

9 0.08%

10

11 Polyox 303 preparation:

12 The polyox, NaCl, and oxide are blended in a Giatt
 13 fluid-bed granulator and sprayed with a 5% HPMC E5
 14 solution in purified water until homogeneous granules
 15 are formed. These granules are passed through 16-mesh
 16 stainless steel screen and mixed with magnesium stearate
 17 and BHT.

18

19 FujiCalin formulations for drug tablet dissolution

20 <u>Formulation</u>	<u>A</u>	<u>B</u>	<u>C</u>	<u>D</u>	<u>E</u>
21					
22 FujiCalin SG	52%	52%	47%	47%	44%
23 Cremophor EL	--	20.6%	18.6%	18.6%	17.6%
24 Cremophor RH	20.6%	--	--	--	--
25 Myvacet 9-45	20.6%	20.6%	18.6%	18.6%	17.6%
26 Progesterone	0.84%	0.84%	0.76%	0.76%	0.72%
27 HPMC E5	4%	4%	4%	4%	4%
28 PVP XL	--	--	10%	--	15%
29 Maltose	--	--	--	10%	--
30 Mg Stearate	1%	1%	1%	1%	1%

31

32 FujiCalin tablet preparation:

1 The progesterone, Cremophor and Myvacet are dissolved by
2 combining the materials in a mixing bowl and mixing with
3 a magnetic stir bar in a 40C water bath for 3 hours.
4 The resulting solution is slowly added to the FujiCalin
5 granules in a mechanical mixing bowl (KitchenAid mixer)
6 while mixing. Mixing is continued for 10 minutes and
7 the HPMC E5, wet granulated with ethanol, is added. The
8 resulting mass is passed through a 20-mesh screen and
9 allowed to dry overnight under ambient conditions. The
10 dried material is again screened through a 20-mesh
11 screen, and the dried granules are blended with the PVP
12 XL on a roller mixer for 10 minutes. Then, the
13 magnesium stearate is added, and the mixture is blended
14 on the roller mixer for an additional 2 minutes. The
15 resulting material is suitable for tableting. To
16 facilitate release of the tablets from the die
17 components, a small amount of mannitol may be applied to
18 the outside surface of the drug formulation being
19 tableted. Tableting is done on a Carver press at one-
20 quarter ton pressure.

21
22 The dissolution profiles for tablets containing the
23 various drug formalities described above in artificial
24 gastric fluid developed in a USP bath are represented in
25 Figure 14, in which circles represent the formulation A,
26 inverted triangles represent formulation B, squares
27 represent formulation C, diamonds represent formulation
28 D, and triangles represent formulation E.

29

30 Pulse System Tableting:

31 Tri-layer tablets containing the foregoing formulations
32 and completed dosage forms are prepared according to the

1 general procedures described in Example 11. The dosage
2 forms provide pulsed delivery of progesterone having
3 varying delay periods depending on the amount of the
4 material in the placebo/barrier layer.

5

6 Neusilin formulations for drug tablet

7	<u>Formulation</u>	<u>G/K</u>	<u>H/L</u>	<u>I/M</u>	<u>J</u>
8					
9	Neusilin US2	34%	36%	38%	40%
10	Cremophor EL	24.99%	26.46%	27.93%	29.4%
11	Myvacet 9-45	24.99%	26.46%	27.93%	29.4%
12	Progesterone	1.02%	1.08%	1.14%	1.2%
13	Acdisol or PVP XL	15%	10%	5%	0%

14

15 Neusilin tablet preparation:

16 Neusilin tablets having formulations as set forth above
17 are prepared in a similar manner to that described for
18 FujiCalin above except that the magnesium stearate and
19 its mixing step are eliminated. Formulations G, H and I
20 are formed with Acdisol. Formulations K, L and M are
21 formed with PVP XL. Tableting is done on a Carver press
22 at one-quarter ton pressure. Tablets are readily
23 ejected from the die without the use of mannitol. The
24 dissolution profiles for the various formulations are
25 represented in Figure 15. The filled circles represent
26 formulation G, filled, inverted triangles represent
27 formulation H, and filled squares represent formulation
28 I. The open circles represent formulation K, open,
29 inverted triangles represent formulation L, and open
30 squares represent formulation M. The filled diamonds
31 represent formulation J.

32

1 Pulse System Tableting:

2 Tri-layer tablets are prepared by the general procedures
3 described in Example 11, and coated with a semipermeable
4 membrane of cellulose acetate/Pluronic F68 at a weight
5 ratio 85/15 as described. Representative release
6 profiles for the tri-layer, pulse dosage forms are
7 illustrated in Figure 16 for formulations as described
8 above with 5% Acdisol, and barrier/membrane layer
9 weights of 50/15 mg, 250/22 mg and 155/16 mg, providing
10 delay periods of about 1, 5 and 10 hours, respectively.

11

12 EXAMPLE 18

13 This example illustrates that the various layers of the
14 dosage forms may be tableted with conventional tableting
15 equipment. The practice formulation, without drug, is
16 prepared as a 10 kg batch for use in a tri-layer dosage
17 form as illustrated in Figure 7. The tri-layer tablets
18 are formed on a multi-station tri-layer tablet press
19 having 11 stations. The press is operated at 5 rpm and
20 the compression forces utilized for the first layer
21 (osmotic push layer), second layer (placebo/particles)
22 and a third layer (barrier) are 100, 100, and 4,000 N
23 respectively. The weights in each tablet of the
24 osmotic/placebo (particles)/barrier layers are
25 175/160/125 mg, respectively. Tablets prepared are
26 expelled from the tableting cavity without sticking to
27 the cavity walls or the punch.

28

29 Neusilin US2	55.8%
30 Cremophor EL	18.6%
31 Myvacet 9-45	18.6%
32 Acdisol	4.5%

1	Stearic Acid	2.0%
2	Mg stearate	0.5%

3

4 Particle layer preparation:

5 In this example drug was not included in the particle
6 layer. The Cremophor and Myvacet are mixed in a large
7 steel pot with a mechanical mixer for 20 minutes. In a
8 large Hobart mixer Neusilin powder is added to the bowl,
9 and the Cremophor/Myvacet blend is slowly added through
10 a funnel to the powder over a 5 minute period while
11 stirring is maintained. Material on the sides of the
12 bowl is scraped down and the blend is mixed for 2
13 minutes more. Then the material is transferred to a
14 Gerrico V-blender, and the Acdisol and stearic acid are
15 added. The resulting mass is mixed for 5 minutes, after
16 which the magnesium stearate is added and the mass mixed
17 for 1 minute more. The blend material flows easily and
18 may be directly loaded into the hoppers of the tableting
19 press.

20

21 Tri-layer tablets prepared from the above formulation as
22 the (drug)/particle layer and the Polyox formulation for
23 the barrier and push layers described above were
24 prepared as described with semipermeable membrane coats
25 formed from 80/20 cellulose acetate/Pluronic F68 of 20
26 mg, 31 mg, 41 mg, and 57 mg and 190 mil exit orifice.
27 The release profiles (measured in terms of Cremophor
28 released since no drug was present) of those systems are
29 presented in Figure 17. The filled circles correspond
30 to a 20 mg membrane coat, filled inverted triangles
31 correspond to a 31 mg membrane coat, filled squares

- 1 correspond to a 41 mg membrane coat, and filled diamonds
- 2 correspond to a 57 mg membrane coat.
- 3

1

2 Claims

3

4 1. A dosage form comprising a plurality of particles
5 having interior pores and a liquid, active agent
6 formulation in the pores, the particles being
7 compactable and adapted to retain substantially all of
8 the liquid active agent formulation within the pores
9 during the compacting process.

10

11 2. A dosage form as claimed in Claim 1 wherein the
12 particles are formed from calcium hydrogen phosphate or
13 magnesium aluminometasilicate..

14

15 3. A dosage form as claimed in Claim 2 wherein the
16 particles are formed from calcium hydrogen phosphate of
17 the following general formula



19 wherein m satisfies the relationship $0 \leq m \leq 2.0$.

20

21 4. A dosage form as claimed in Claim 3 wherein the
22 particles are formed by spray drying a scale-like
23 calcium hydrogen phosphate with a specific surface area
24 of $20 \text{ m}^2/\text{g}$ to $60 \text{ m}^2/\text{g}$, an apparent specific volume of
25 1.5 ml/g or more, an oil absorption capacity of 0.7
26 ml/g or more, a primary particle size of 0.1μ to 5μ ,
27 and an average particle size of 2μ to 10μ among
28 secondary particles that are aggregates of the primary
29 particles.

30

31 5. A dosage form as claimed in Claim 3 or 4 wherein
32 the particles are calcium hydrogen phosphate having a

1 specific volume of at least 1.5 ml/g, a BET specific
2 area of at least 20 m²/g, and a water absorption
3 capacity of at least 0.7 ml/g.

4

5 6. A dosage form as claimed in any one of Claims 3 to
6 5 wherein the particles having a size distribution of
7 100% less than 40 mesh, 50%-100% less than 100 mesh and
8 10%-60% less than 200 mesh.

9

10 7. A dosage form as claimed in Claim 6 wherein the
11 particles have a size distribution of which 100% are
12 less than 40 mesh, 60%-90% are less than 100 mesh and
13 20%-60% are less than 200 mesh.

14

15 8. A dosage form as claimed in any one of the
16 preceding Claims wherein the particles have a bulk
17 density of 0.4-0.6 g/ml, a BET surface area of 30-
18 50 m²/g, a specific volume of greater than 1.5 ml/g, and
19 a mean pore size of at least 50 Angstroms.

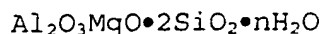
20

21 9 A dosage form as claimed in Claim 3 wherein the
22 particles are calcium hydrogen phosphate having a bulk
23 specific volume of 1.5 ml/g-5 ml/g, a BET specific area
24 of 20 m²/g-60 m²/g, a water absorption capacity of at
25 least 0.7 ml/g, and a mean particle size of at least 70
26 microns.

27

28 10. A dosage form as claimed in Claim 2 wherein the
29 particles are magnesium aluminometasilicate represented
30 by the general formula

31



32

1 wherein n satisfies the relationship $0 \leq n \leq 10$.

2

3 11. A dosage form as claimed in Claim 10 wherein the
4 particles comprise magnesium aluminometasilicate
5 powder.

6

7 12. A dosage form as claimed in any one of Claims 1 to
8 11 wherein the particles are formed from FujiCalin®,
9 Neusilin™, or a combination thereof.

10

11 13. A dosage form as claimed in any one of the
12 preceding Claims wherein the dosage form includes a pH
13 regulating agent selected from one or more of the group
14 comprising organic acids, inorganic acids and bases.

15

16 14. A dosage form as claimed in any one of the
17 preceding Claims wherein the dosage form includes a
18 chelating agent.

19

20 15. A dosage form as claimed in any one of the
21 preceding Claims wherein the particles are formed from
22 FujiCalin® and the dosage form includes an organic
23 acid, chelating agent, or a combination thereof.

24

25 16. A dosage form as claimed in any one of the
26 preceding Claims wherein the weight percent of liquid,
27 active agent formulation is at least 5% of the total
28 weight of the dosage form.

29

30 17. A dosage form as claimed in any one of the
31 preceding Claims wherein the dosage form is adapted for

1 rapid release of the liquid, active agent formulation .
2 upon administration to a subject.

3

4 18. A dosage form as claimed in any one of the
5 preceding Claims wherein the active agent is selected
6 from active agents that have low water solubility.

7

8 19. A dosage form as claimed in Claim 18 wherein the
9 active agent is sildenafil citrate, acetaminophen,
10 ibuprofen or ketoprofen.

11

12 20. A dosage form as claimed in any one of the
13 preceding claims where the particles are able to bind
14 themselves in a dosage form.

15

16 21. A dosage form as claimed in any one of the
17 preceding Claims being in the form of a gelatin
18 capsule, the particles being dispersed in a liquid to
19 form a paste adapted for loading into a gelatin
20 capsule, and the particles being calcium hydrogen
21 phosphate having a specific volume of at least
22 1.5 ml/g, a BET specific area of at least 20 m²/g, and a
23 water absorption capacity of at least 0.7 ml/g; or
24 magnesium aluminometasilicate.

25

26 22. A dosage form as claimed in Claim 21 wherein liquid
27 forming the paste with the particles is the same liquid
28 as the liquid of the liquid, active agent formulation.

29

30 23. A dosage form as claimed in any one of Claims 1 to
31 16 wherein the particles are adapted to be dispersed in
32 a bioerodible carrier.

1

2 24. A dosage form as claimed in Claim 23 wherein the
3 bioerodible carrier swells upon imbibing fluid from
4 stomach so as to be retained within the stomach of a
5 subject for a prolonged period of time.

6

7 25. A dosage form as claimed in Claims 23 or 24 wherein
8 the bioerodible carrier comprises a polymer matrix
9 formed of a mixture of a swellable, water soluble
10 polymer that expands when in contact with fluids in the
11 gastric environment and a hydroattractant.

12

13 26. A dosage form as claimed in Claim 25 wherein the
14 matrix is formed with a rigid or semi-rigid segment in
15 which swelling of the matrix is constrained to provide
16 a rigid or semi-rigid section in the dosage form that
17 facilitates the dosage form remaining in the stomach of
18 a subject over a prolonged period of time.

19

20 27. A dosage form as claimed in Claim 26 wherein the
21 rigid or semi-rigid section of the dosage form
22 comprises one or more insoluble materials, having low
23 water permeability and formed as a band circumscribing
24 a portion of the surface of the matrix, that along with
25 the banded portion of the polymer matrix forms the
26 rigid or semi-rigid segment of the dosage form.

27

28 28. A dosage form as claimed in any one of Claims 23 to
29 27 wherein the dosage form comprises (a) a
30 therapeutically-effective amount of a liquid, active
31 agent formulation sorbed into porous particles, (b) a
32 polymer matrix in which the porous particles are

1 dispersed, the polymer matrix including a high
2 molecular weight, water-soluble polymer and a
3 hydroattractant, the polymer matrix having an outer
4 surface for exposure to the environment of use, and (c)
5 a band of insoluble material circumscribing a portion
6 of the outer surface of the polymer matrix.

7
8 29. A dosage form as claimed in Claim 28 wherein the
9 hydroattractant is a water-insoluble polymer, and the
10 polymer matrix further includes non-polymeric water-
11 soluble excipients and polymers of molecular weight of
12 less than 10,000 grams per mole.

13
14 30. A dosage form as claimed in Claim 28 or Claim 29
15 wherein the weight percent of the water soluble, high
16 molecular weight polymer is about 10 to 50 weight
17 percent and the weight percent of the hydroattractant
18 is about 5 to 70 weight percent.

19
20 31. A dosage form as claimed in any one of Claims 23 to
21 30 which comprises a unitary compressed dispersion of a
22 liquid, active agent formulation in a plurality of
23 porous particles in a gel-forming, erodible polymer
24 matrix having a first portion that swells in the
25 stomach while maintaining its physical integrity for a
26 prolonged period of time and a second, non-erodible,
27 non-gel-forming portion for promoting retention of the
28 dosage form in the stomach over a prolonged period of
29 time.

30
31 32. A dosage form as claimed in any one of Claims 25 to
32 31 wherein the number average molecular weight of the

1 water-soluble polymer is between about 100,000 and
2 20,000,000 grams per mole.

3
4 33. A dosage form as claimed in Claim 32 wherein the
5 water soluble polymer is one or more of the group
6 comprising polyethylene oxide, hydroxypropyl cellulose,
7 hydroxypropyl methyl cellulose, hydroxyethyl cellulose,
8 sodium carboxy methylcellulose, calcium carboxymethyl
9 cellulose, methyl cellulose, polyacrylic acid,
10 maltodextrin, pre-gelatinized starch or polyvinyl
11 alcohol.

12
13 34. A dosage form as claimed in any one of Claims 25 to
14 33 wherein the hydroattractant is one or more of the
15 group comprising low-substituted hydroxypropyl
16 cellulose, microcrystalline cellulose, cross-linked
17 sodium or calcium carboxymethyl cellulose, cellulose
18 fiber, cross-linked polyvinyl pyrrolidone, cross-linked
19 polyacrylic acid, cross-linked Amberlite resin,
20 alginates, colloidal magnesium-aluminum silicate, corn
21 starch granules, rice starch granules, potato starch
22 granules or sodium carboxymethyl starch.

23
24 35. A dosage form as claimed in any one of Claims 23 to
25 34 adapted for gastric retention.

26
27 36. A dosage form as claimed in any one of Claims 23 to
28 35 wherein the active agent is one or more of the group
29 comprising an antiviral, antimicrobial, antidiabetic,
30 antihyperglycemic, hypoglycemic, antidepressant,
31 antiobesity, immunosuppressive, or antifungal active
32 agent.

1

2 37. A dosage form as claimed in Claim 36 wherein the
3 active agent is one or more of the group comprising
4 acyclovir, ganciclovir, cimetidine, ranitidine,
5 captopril, methyldopa, selegiline, minocycline,
6 metformin, bupropion, orlistat, cyclosporin,
7 cyclosporine metformin or fexofenadine or a
8 pharmaceutically acceptable salt thereof.

9

10 38. A dosage form as claimed in any one of Claims 23 to
11 37 wherein the active agent is released from the porous
12 particles in a liquid formulation to the
13 gastrointestinal tract over a time period of at least 3
14 hours.

15

16 39. A dosage form as claimed in any one of Claims 23 to
17 38 comprising a gastric-emptying delaying agent.

18

19 40. A dosage form as claimed in Claim 39 wherein the
20 gastric-emptying delaying agent is selected from
21 anticholinergic agents, methylcellulose, guar gum, fats
22 and fatty acids of 10-15 carbon atoms.

23

24 41. A dosage form as claimed in any one of Claims 23 to
25 40 adapted to be retained within the stomach of a
26 subject for a prolonged period of time for sustained
27 release of the liquid, active agent formulation.

28

29 42. A dosage form for an active agent comprising a wall
30 defining a cavity, the wall having an exit orifice
31 formed or formable therein and at least a portion of
32 the wall being semipermeable; an expandable layer

1 located within the cavity remote from the exit orifice
2 and in fluid communication with the semipermeable
3 portion of the wall; a drug layer located within the
4 cavity adjacent the exit orifice and in direct or
5 indirect contacting relationship with the expandable
6 layer, wherein the drug layer is a form defined by the
7 dosage forms of any one of Claims 1 to 16.

8

9 43. A dosage form as claimed in Claim 42 having a
10 placebo layer between the exit orifice and the drug
11 layer.

12

13 44. A dosage form as claimed in Claim 42 or Claim 43
14 having a flow-promoting layer interposed between the
15 inner surface of the wall and at least the external
16 surface of the drug layer located within the cavity.

17

18 45. A dosage form as claimed in any one of Claims 42 to
19 44, having at least two drug layers separated by at
20 least one inert layer.

21

22 46. A dosage form as claimed in any one of Claims 42 to
23 45 having at least two drug layers, each of said drug
24 layers containing a different active agent.

25

26 47. A dosage form as claimed in any one of Claims 42 to
27 44 wherein the liquid, active agent formulation of the
28 drug layer comprises a self-emulsifying formulation.

29

30 48. A dosage form as claimed in Claim 47 wherein the
31 active agent has low water solubility.

32

1 49. A dosage form as claimed in any one of Claims 42 to
2 48 wherein the liquid active agent of the drug layer
3 comprises an absorption enhancer.

4

5 50. A dosage form as claimed in any one of Claims 42 to
6 49 wherein the liquid, active agent formulation
7 comprises at least 30% by weight of the drug layer.

8

9 51. A dosage form as claimed in any one of Claims 42 to
10 50 adapted for sustained release of the liquid, active
11 agent formulation upon administration to a subject.

12

13 52. A dosage form as claimed in any one of Claims 42 to
14 50 adapted for pulsatile release of the liquid, active
15 agent formulation upon administration to a subject.

16

17 53. A dosage form as claimed in any one of the
18 preceding Claims wherein the dosage form is a unitary
19 and oral dosage form.

20

21 54. A dosage form as claimed in any one of claims 1,
22 13, 14, 16-20 and 23-53, wherein the particles are
23 formed from microcrystalline cellulose or silicon
24 dioxide.

25

26 55. A composition comprising from about 1 to 50 weight
27 percent of porous calcium hydrogen phosphate particles
28 having sorbed therein a liquid, active agent
29 formulation, about 5 weight percent to about 50 weight
30 percent of a polyethylene oxide polymer having a number
31 average molecular weight of between about 100,000 and
32 20,000,000 grams per mole and about 5 weight percent to

1 about 60 weight percent of a hydroxypropyl cellulose
2 polymer having a hydroxypropyl content of between about
3 10 weight percent and about 13 weight percent of the
4 hydroxypropyl cellulose polymer the porous particles
5 comprising calcium hydrogen phosphate with a specific
6 surface area of $20 \text{ m}^2/\text{g}$ to $60 \text{ m}^2/\text{g}$, an apparent specific
7 volume of 1.5 ml/g or more, an oil absorption capacity
8 of 0.7 ml/g or more, and a mean particle size of
9 greater than 70 microns, the calcium hydrogen phosphate
10 being represented by the following general formula:



12 wherein m satisfies the relationship $0 \leq m \leq 2.0$.

13
14 56. A composition comprising a liquid formulation of
15 the active agent sorbed into a plurality of porous
16 particles, the particles being formed by spray drying a
17 scale-like calcium hydrogen phosphate with a specific
18 surface area of $20 \text{ m}^2/\text{g}$ to $60 \text{ m}^2/\text{g}$, an apparent specific
19 volume of 1.5 ml/g or more, an oil absorption capacity
20 of 0.7 ml/g or more, a primary particle size of 0.1μ to
21 5μ , and an average particle size of 2μ to 10μ among
22 secondary particles that are aggregates of the primary
23 particles, the scale-like calcium hydrogen phosphate
24 being represented by the following general formula:



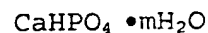
26 wherein m satisfies the relationship $0 \leq m \leq 2.0$, and
27 dispersed throughout a bioerodible carrier, the
28 particles being released in the environment of use over
29 a prolonged period of time.

30

31 57. A method of manufacturing a dosage form comprising
32 contacting a plurality of particles having interior

1 pores as defined in any one of Claims 1 to 11 with a
2 liquid, active agent formulation, and compacting the
3 particles into a dosage form without removing all of
4 the liquid from the liquid, active agent formulation.

5
6 58. A method as claimed in Claim 57 wherein the
7 particles are spherical calcium hydrogen phosphate
8 particles obtained by spray drying a scale-like calcium
9 hydrogen phosphate with a specific surface area of 20
10 m^2/g to 60 m^2/g , an apparent specific volume of 1.5 ml/g
11 or more, an oil absorption capacity of 0.7 ml/g or
12 more, a primary crystal particle size of 0.1μ to 5μ ,
13 and an average particle size of 2μ to 10μ among
14 secondary particles that are aggregates of the primary
15 particles, the scale-like calcium hydrogen phosphate
16 being represented by the following general formula:



17
18 wherein m satisfies the relationship $0 \leq m \leq 2.0$.

19
20 59. A method as claimed in Claim 56 or 57 in which less
21 than 80% of the liquid of the active agent formulation
22 is removed prior to the compacting step.

23
24 60. A method of facilitating the release of an active
25 agent from a dosage form comprising sorbing a liquid
26 formulation of the active agent into a plurality of
27 porous particles, the particles being formed as defined
28 in Claim 58 and dispersing the particles throughout a
29 bioerodible carrier.

30
31 61. A method for facilitating rapid release of an
32 active agent from a dosage form containing a liquid,

1 active agent formulation sorbed into a porous particle,
2 wherein the dissolution rate of the porous particle is
3 pH sensitive, comprising incorporating a pH regulating
4 agent into the dosage form to bias the pH of the
5 microenvironment of the porous particle after
6 administration toward a pH increasing the rate of
7 dissolution of the porous particle.

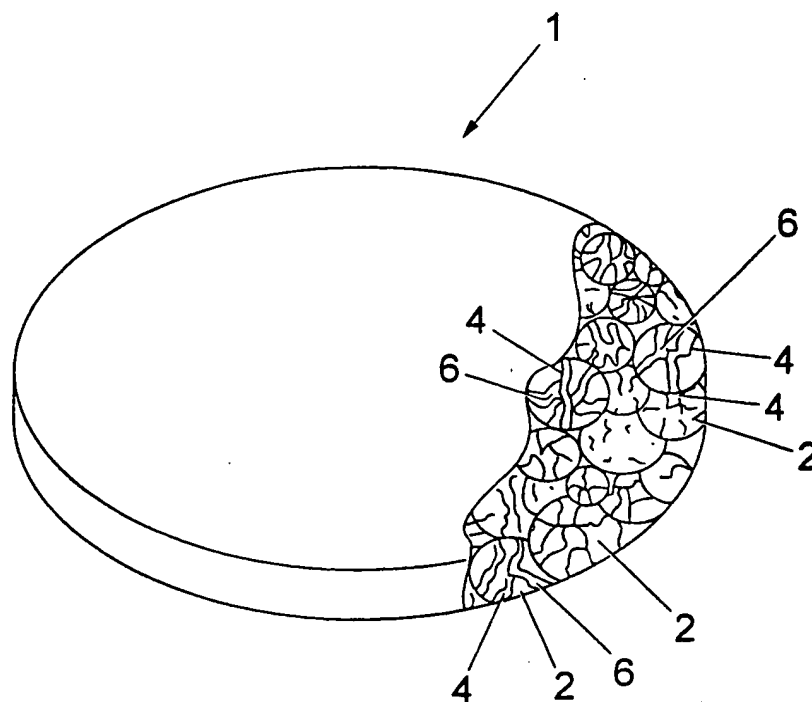
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9 62. A method as claimed in Claim 61 wherein the pH
10 regulating agent is an organic acid, an inorganic acid
11 or a base.

12

13 63. A method as claimed in Claim 61 or Claim 62 wherein
14 the particle is a calcium hydrogen phosphate and the pH
15 regulating agent is an organic acid.

1 / 15

*Fig. 1*

2 / 15

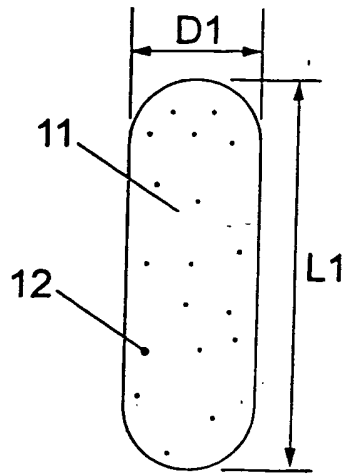


Fig. 2a

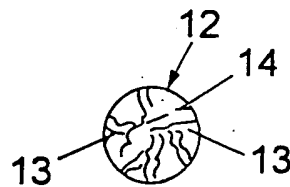


Fig. 2c

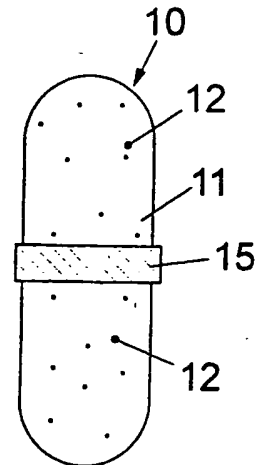


Fig. 2b

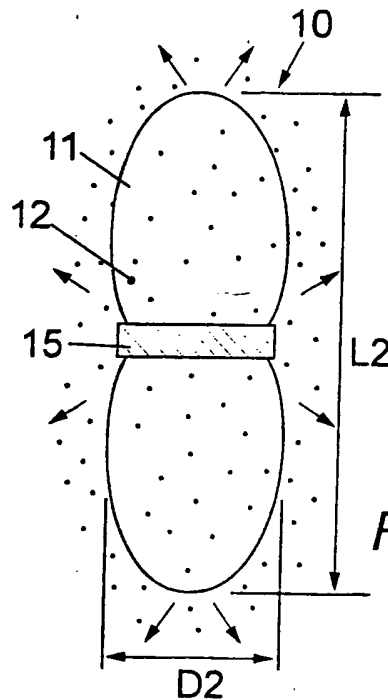


Fig. 3

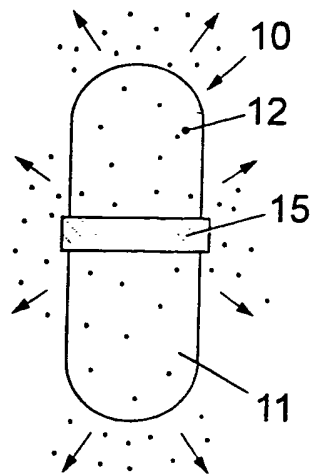


Fig. 4a

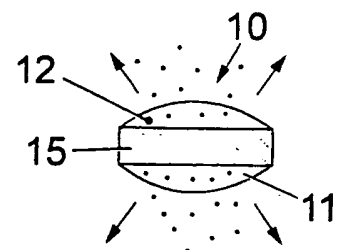
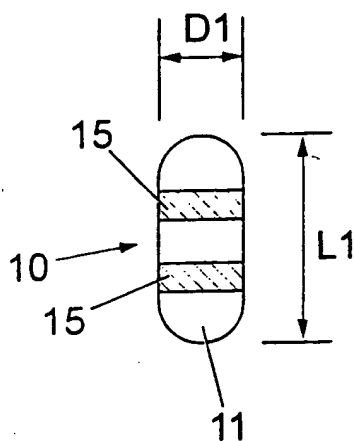
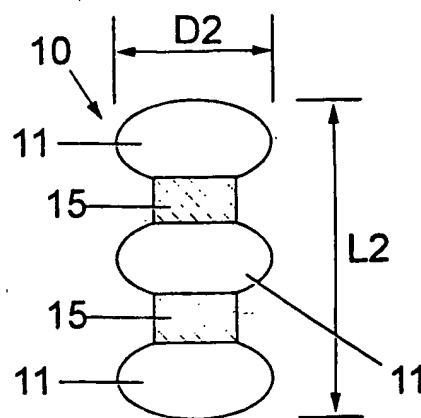
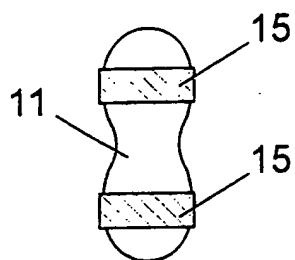
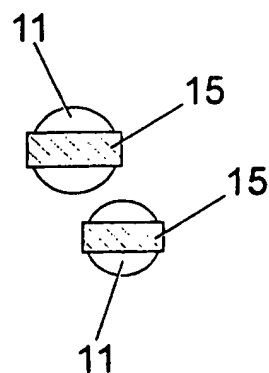


Fig. 4b

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*Fig. 5a**Fig. 5b**Fig. 5c**Fig. 5d*

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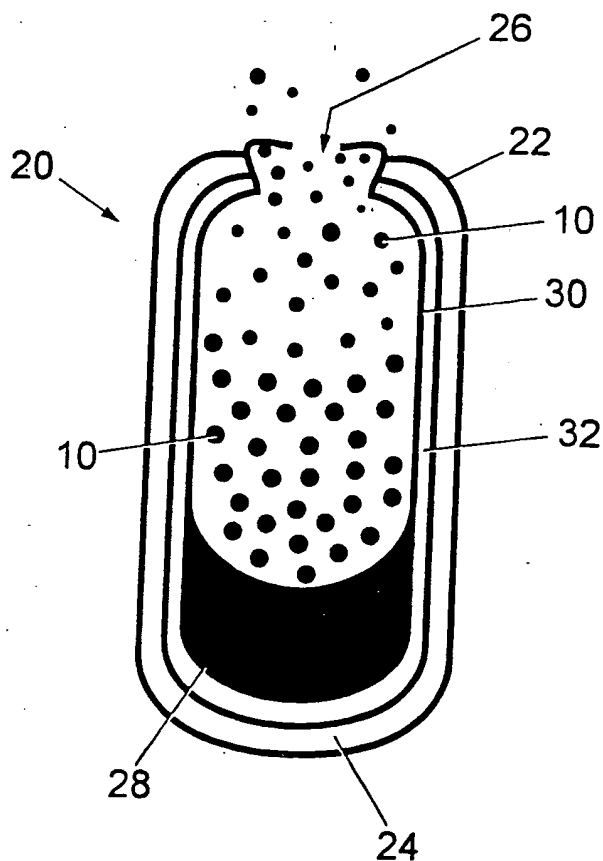
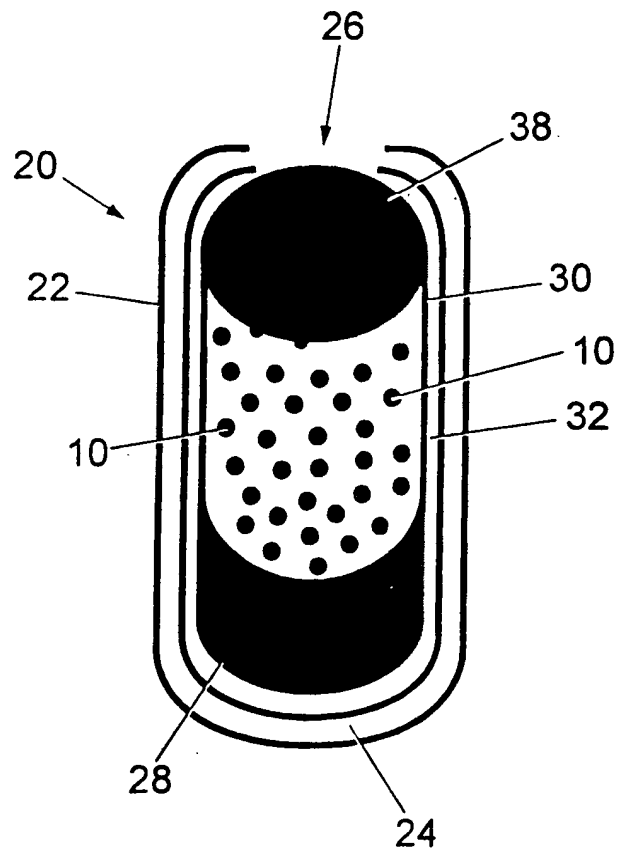


Fig. 6

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*Fig. 7*

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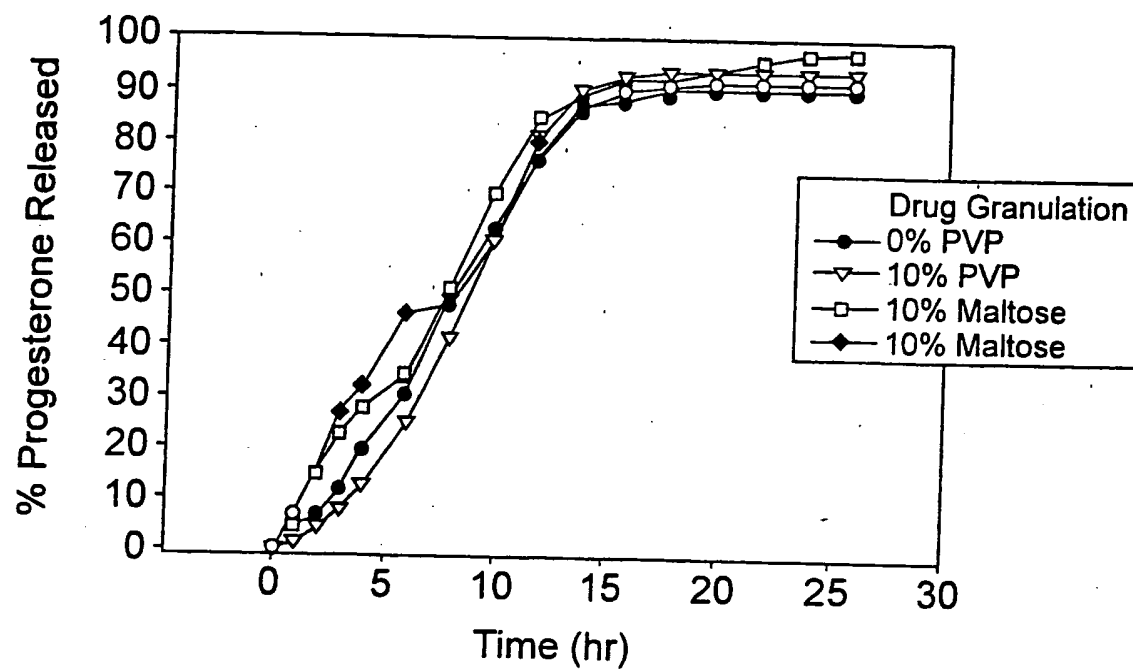
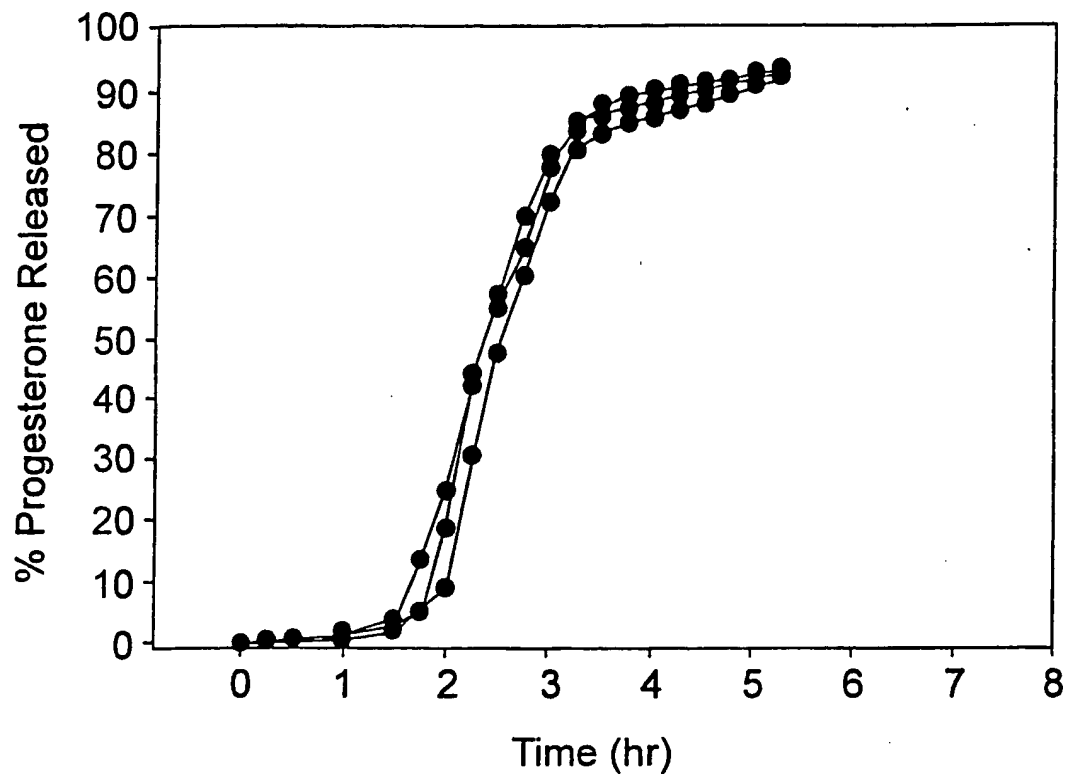
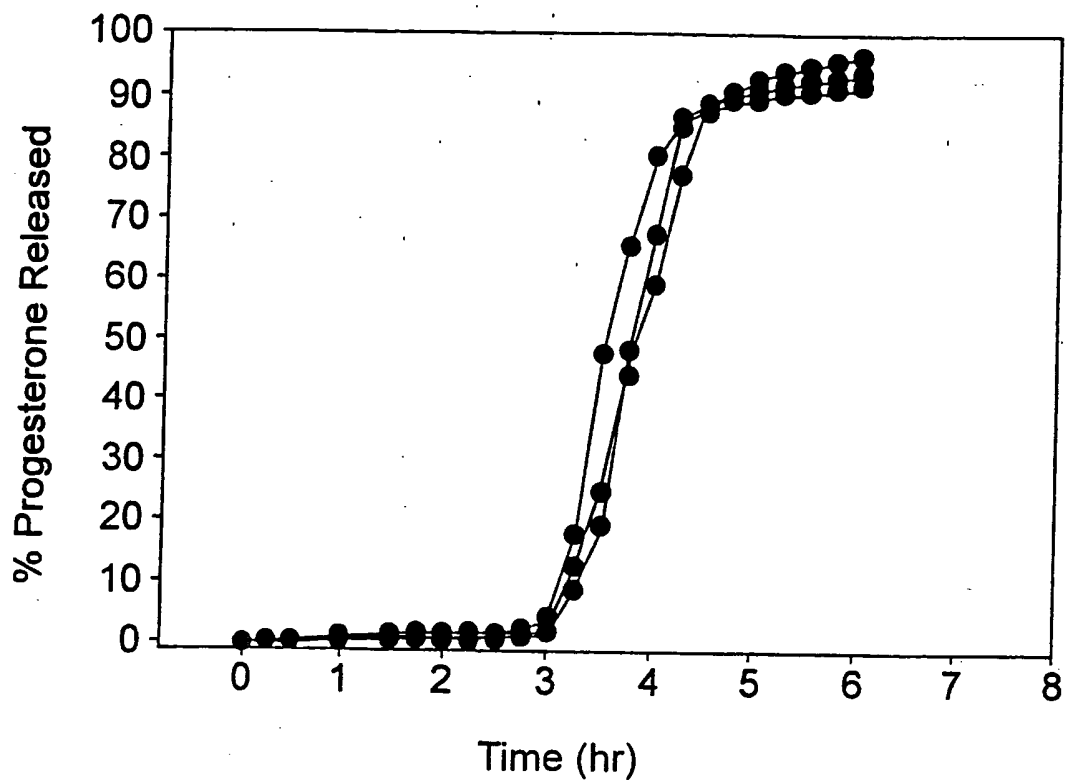


Fig. 8

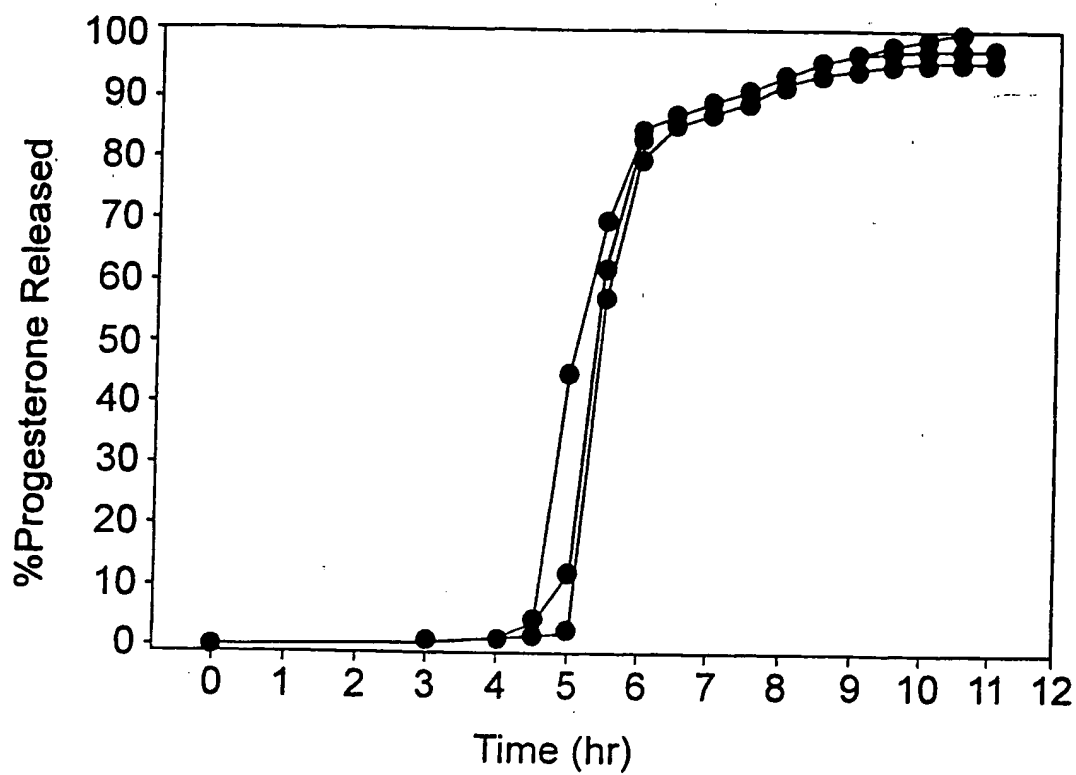
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*Fig. 9*

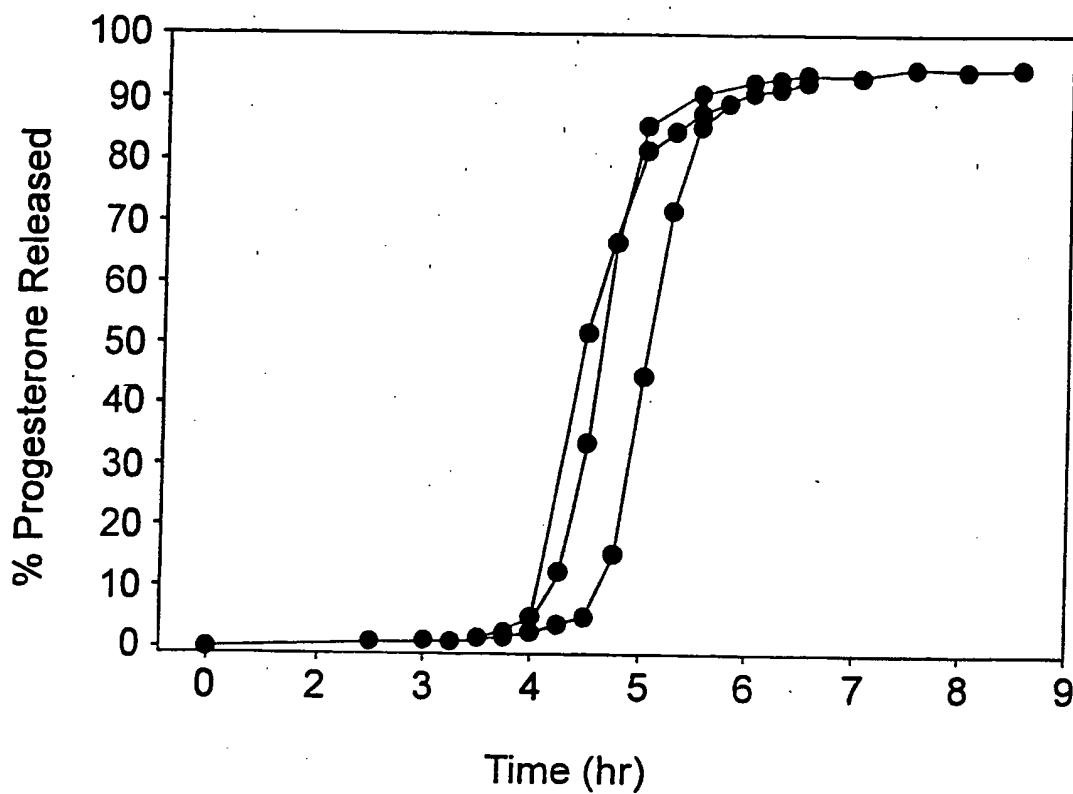
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*Fig. 10*

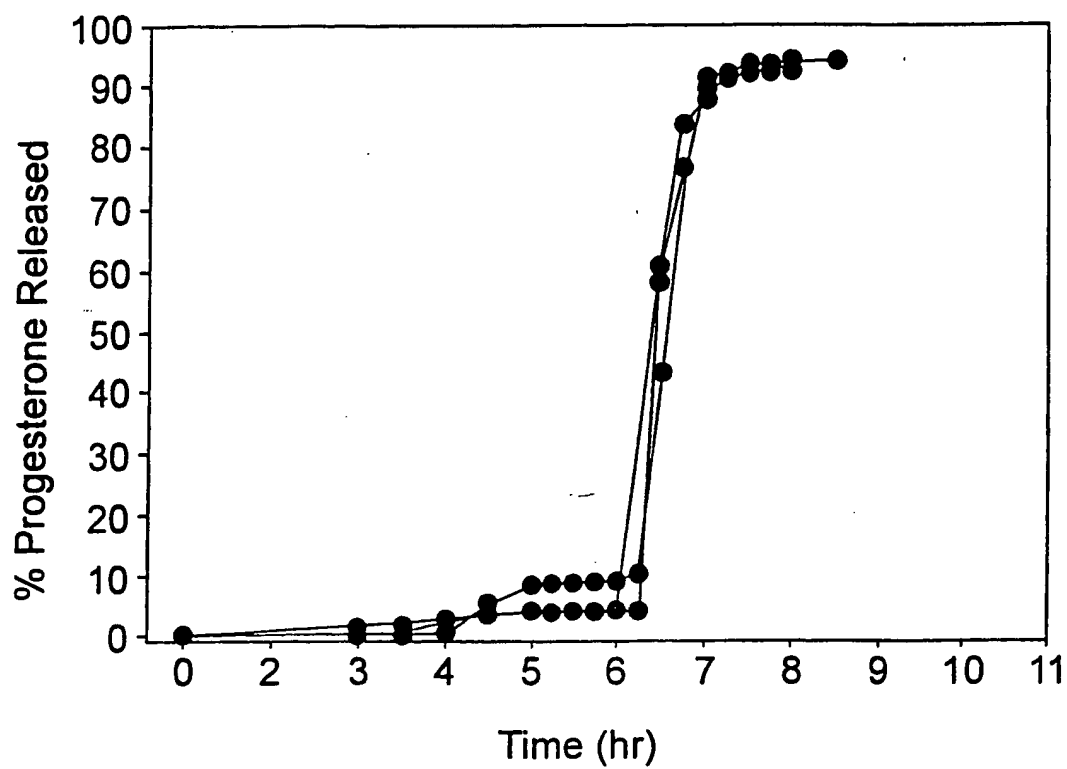
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*Fig. 11*

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*Fig. 12*

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*Fig. 13*

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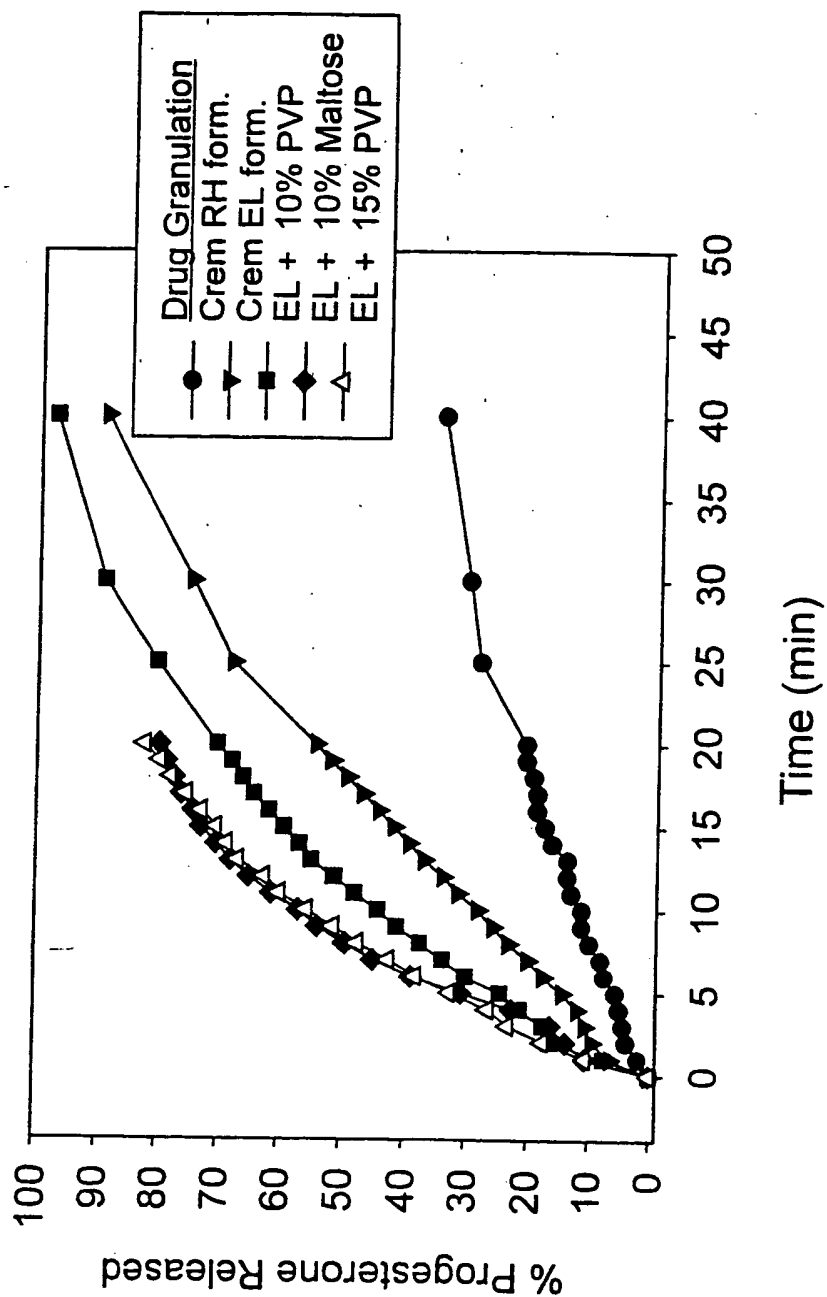
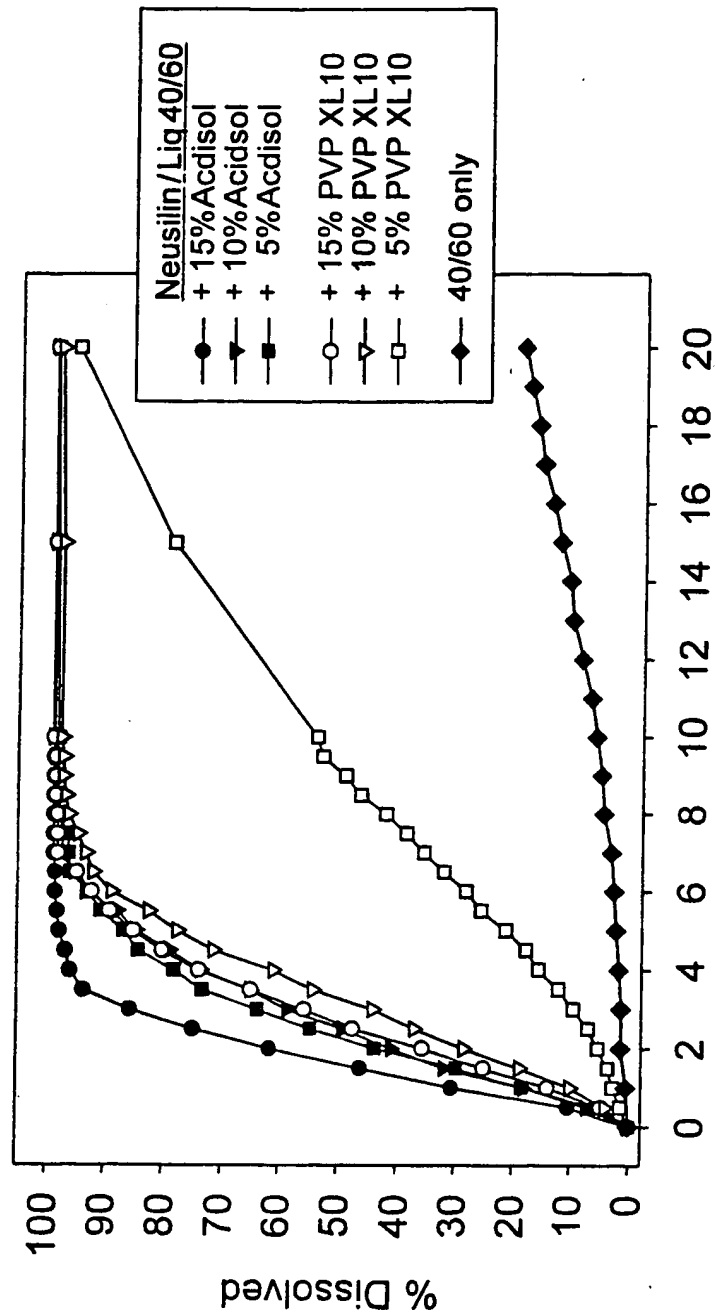


Fig. 14

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Time (min)

Fig. 15

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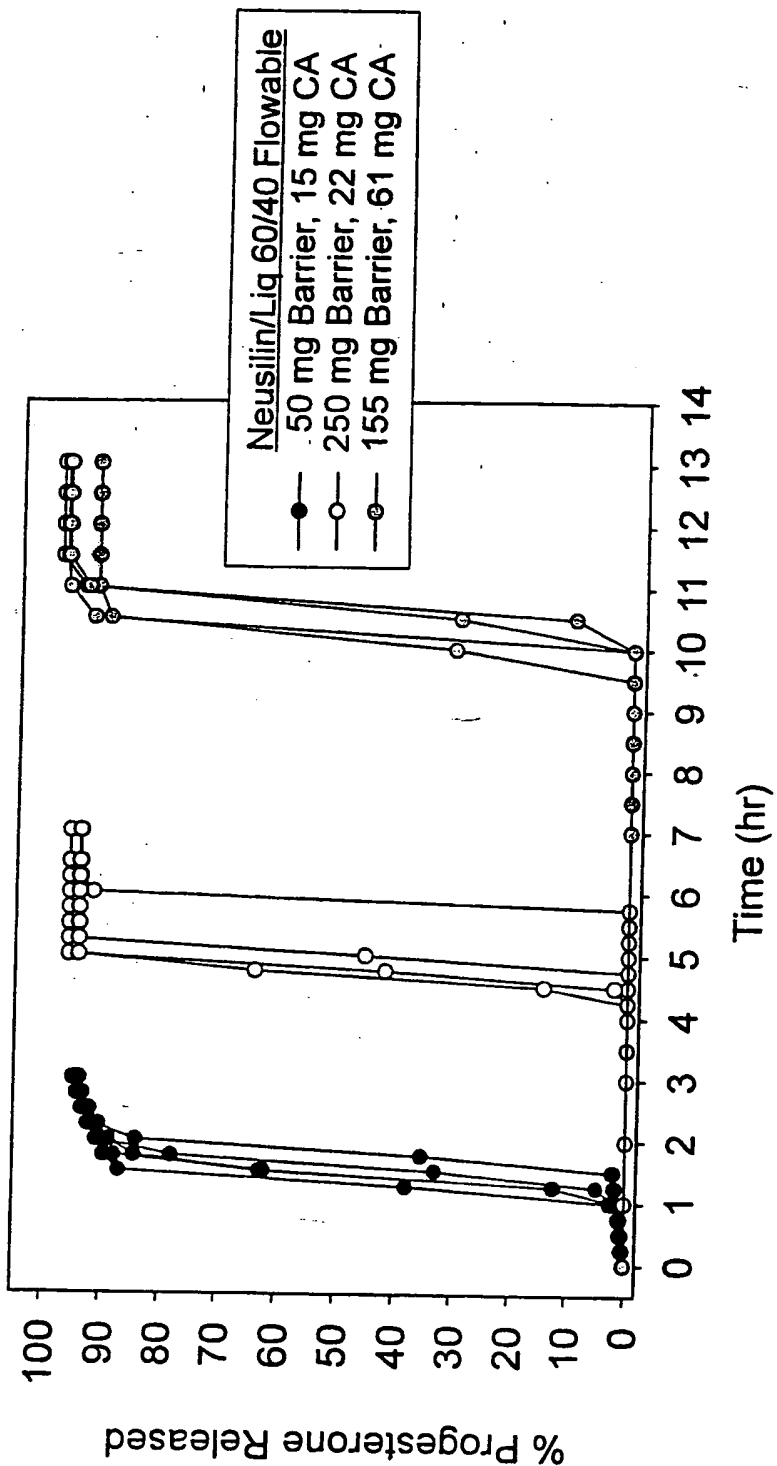


Fig. 16

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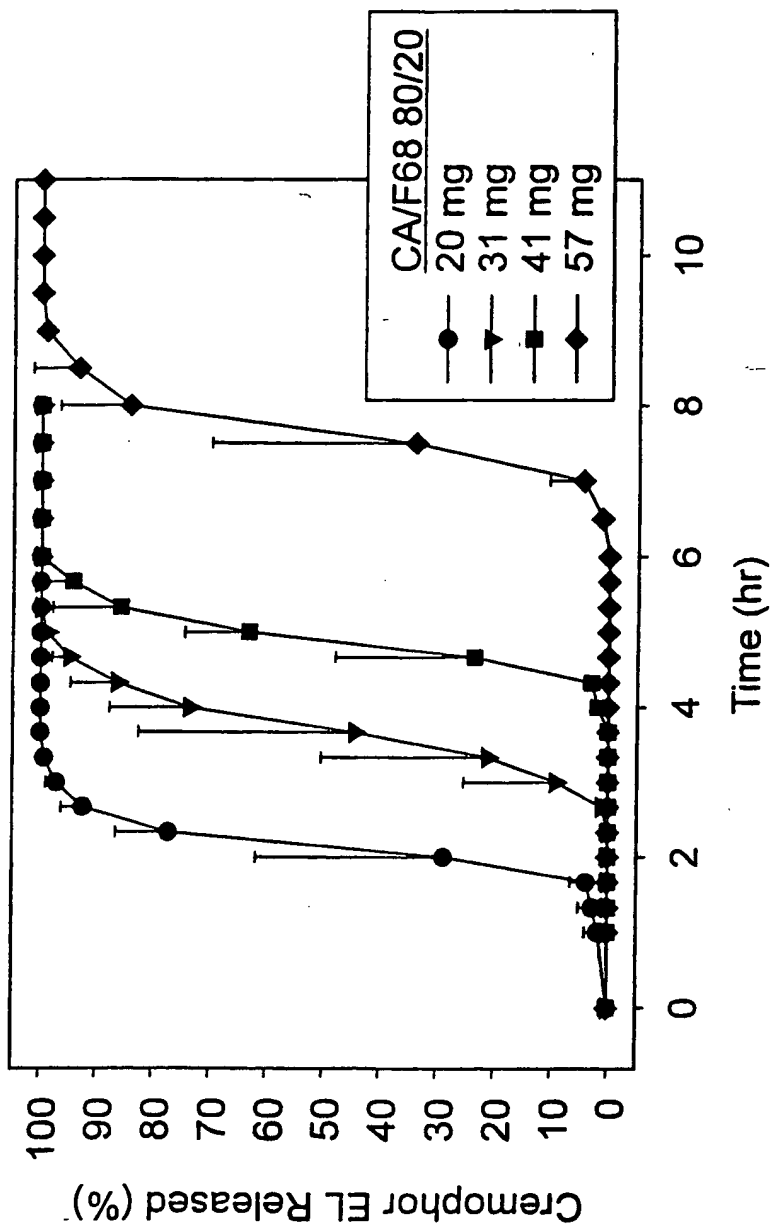


Fig. 17

INTERNATIONAL SEARCH REPORT

Int. National Application No.

PCT/GB 99/04426

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/16 A61K9/26 A61K9/48 A61K9/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 98 38987 A (SANOFI WINTHROP INC) 11 September 1998 (1998-09-11)</p> <p>page 4, line 21 -page 5, line 15 page 14, line 17 -page 15, line 11; example 5 claims 1,4,7</p> <p style="text-align: center;">— -/-</p>	<p>1-3,13, 16-18, 20, 23-27, 32-36, 38,41, 53,54, 57,59, 61,62</p>

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

10 May 2000

Date of mailing of the international search report

17/05/2000

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Epskamp, S

INTERNATIONAL SEARCH REPORT

In International Application No.

PCT/GB 99/04426

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>EP 0 448 091 A (GREEN CROSS CORP) 25 September 1991 (1991-09-25)</p> <p>page 2, line 19 - line 34 page 10, line 20 - line 32 page 10, line 46 - line 52 examples 5-7 claims 1,5-7,9,14-16</p>	<p>1,2, 10-12, 16-18, 20, 23-27, 32-35, 38,41, 53,54, 57,59</p>
X	<p>US 5 800 834 A (BOLTON SANFORD M ET AL) 1 September 1998 (1998-09-01) cited in the application</p> <p>column 2, line 55 -column 3, line 3 column 5, line 1 - line 40; figure 1 column 11, line 31 -column 12, line 33 column 14, line 25 - line 45 column 16, line 15 -column 19, line 40; tables 3-7 claims</p>	<p>1,16-18, 20, 23-27, 32-36, 38,41, 53,54, 57,59</p>
X	<p>EP 0 163 178 A (BEECHAM GROUP PLC) 4 December 1985 (1985-12-04)</p> <p>page 1, paragraph 4 -page 2, paragraph 6 page 3, paragraph 2 -page 4, paragraph 2 page 5, paragraphs 6,7 examples claims</p>	<p>1,16-18, 20, 23-27, 32-36, 38,41, 53,54, 57,59</p>
A	<p>US 5 486 365 A (TAKADO KANEMASA ET AL) 23 January 1996 (1996-01-23) cited in the application column 1, line 6 - line 11 column 2, line 4 - line 33 column 4, line 14 - line 21 column 6; example 11 claims</p> <p style="text-align: center;">--- -/--</p>	<p>1-9,12</p>

INTERNATIONAL SEARCH REPORT

Int. Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 155 889 A (ALZA CORP) 2 October 1985 (1985-10-02) page 1, line 106 -page 2, line 18; figures page 7, line 6 - line 89 claims	42-52
P,X	US 5 955 086 A (DELUCA DARYL L ET AL) 21 September 1999 (1999-09-21) column 4, line 20 -column 5, line 6 example claims 1,4,6,8,9	1-3, 16-18, 20, 23-27, 32-36, 38,41, 53,57,59
E	EP 0 985 411 A (MCNEIL PPC INC) 15 March 2000 (2000-03-15) paragraphs '0005!-'0007! paragraphs '0011!,'0019!-'0025! examples 1-3 claims	1,2, 10-12, 16-18, 20, 23-27, 32-36, 38,41, 53,54, 57,59

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